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OPHTHALMOLOGY

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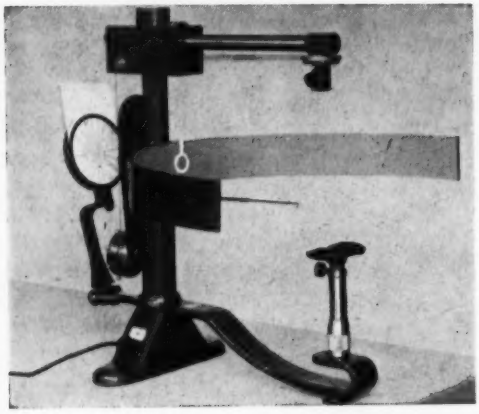

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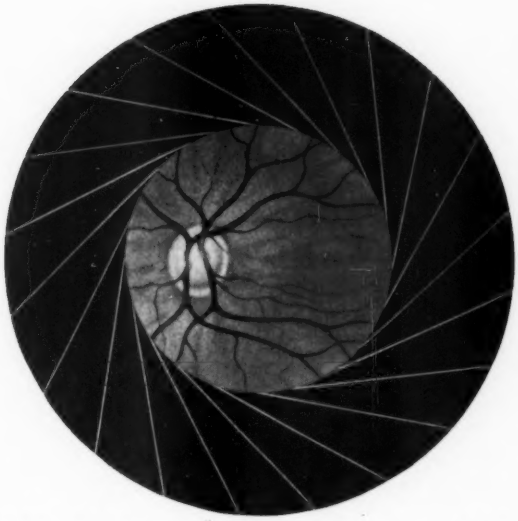

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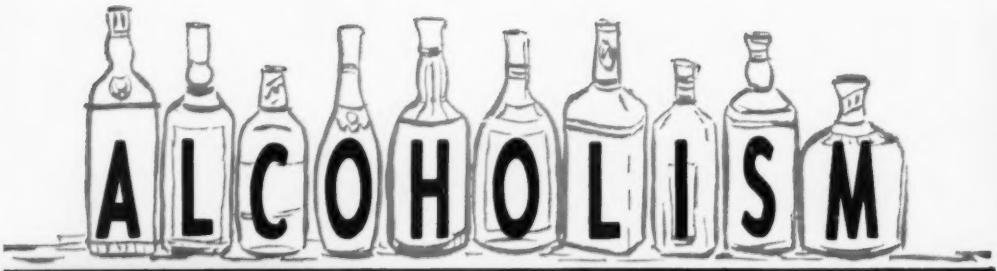

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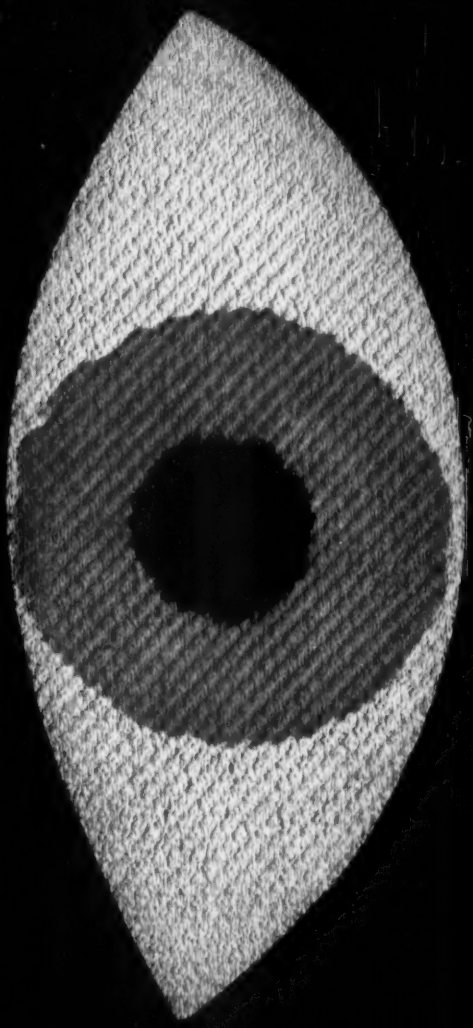

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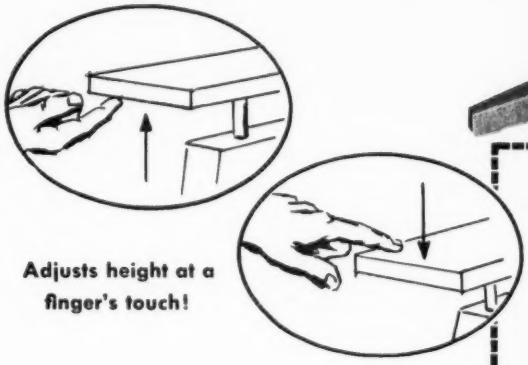

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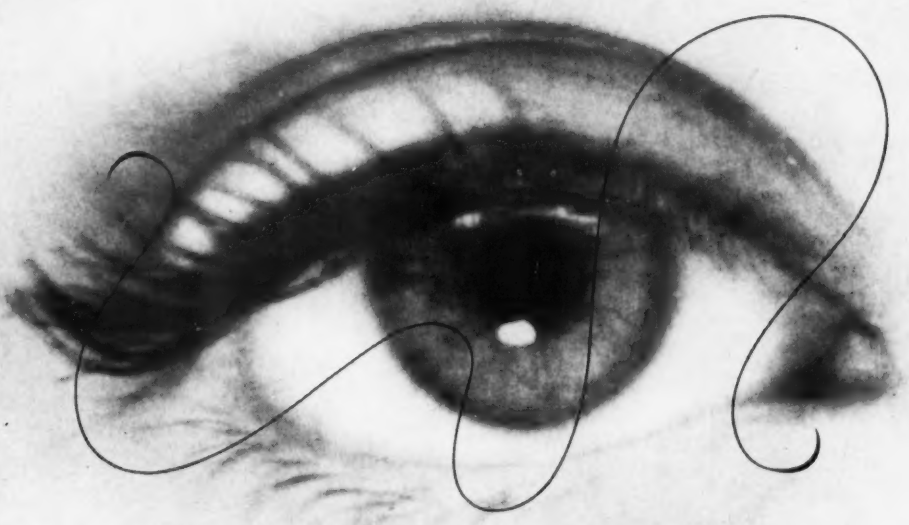

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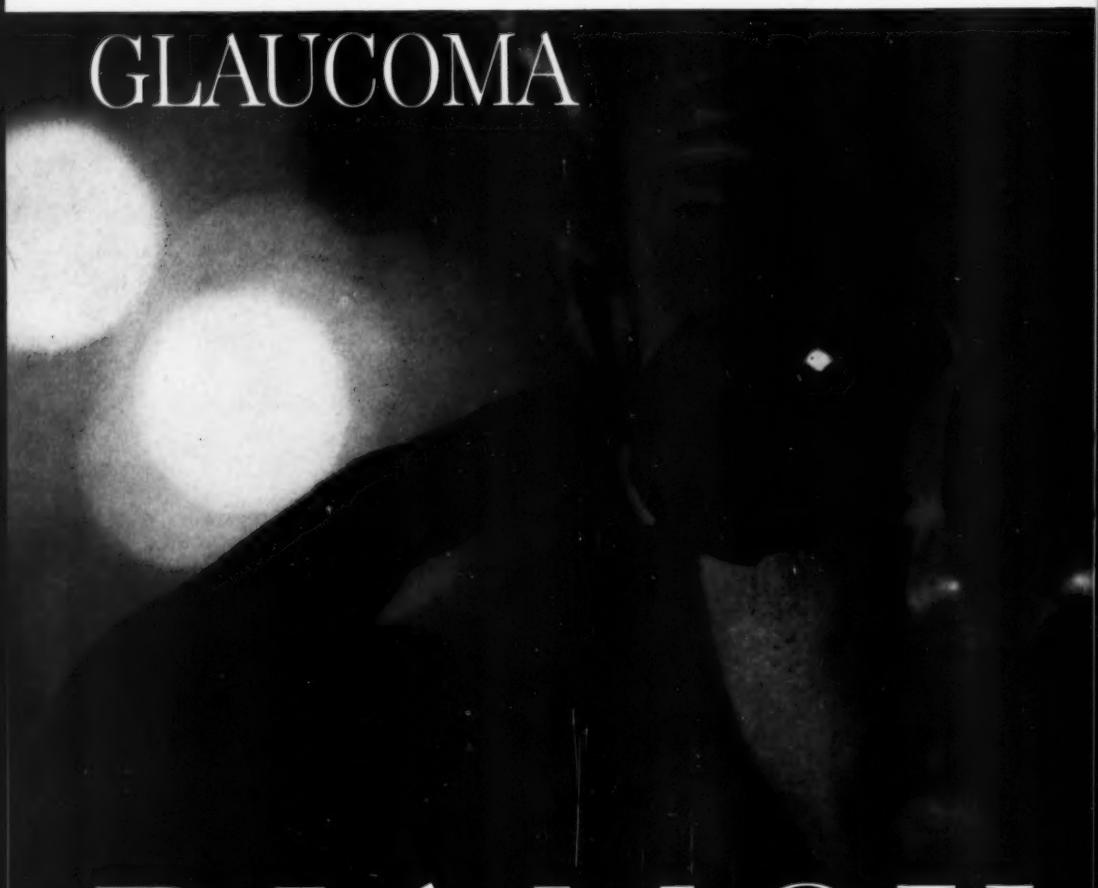

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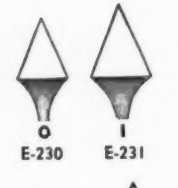

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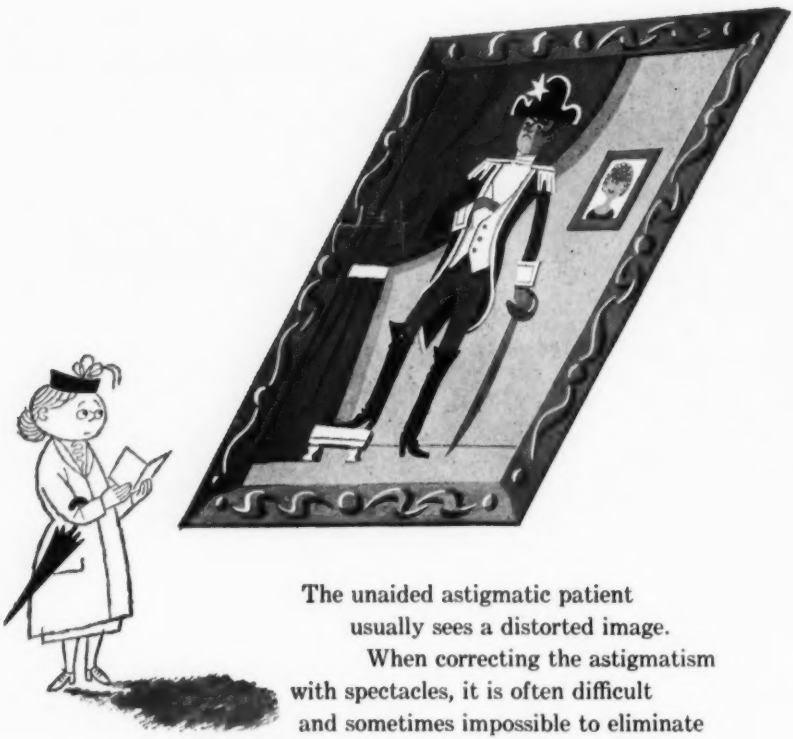

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HIGHLIGHTS FROM THE A.M.A. COUNCIL ON DRUGS

REPORT ON TRIAMCINOLONE

J.A.M.A. 169:257 (January 17) 1959.

"It [triamcinolone] has an anti-inflammatory potency greater than an equal amount of prednisolone; i.e., comparable suppressive effects may usually be achieved with lower doses of triamcinolone than with prednisolone."

"Triamcinolone lacks the sodium-retaining and edema-producing effects of most other glucocorticoids. During the first several days of administration, it may cause a loss of sodium from the body; an initial mild diuretic action is frequently observed, whether the patient is frankly edematous or not. This is in contrast to the definite sodium-retaining and fluid-retaining properties of cortisone and hydrocortisone and to a much lesser extent with prednisone and prednisolone."

"Except in exceedingly large doses, triamcinolone apparently has no consistent effect on potassium excretion. Hence, neither sodium restriction nor potassium supplementation is ordinarily required during therapy with this agent."

"As with other glucocorticoids, the long-term administration of triamcinolone results in definite catabolic effects, as indicated by impairment of carbohydrate utilization and negative protein and calcium balance. This catabolic effect, coupled with a lack of appetite stimulation which is apparently peculiar to triamcinolone, may produce weight loss that might be undesirable in some patients treated for long periods of time."

"...the voracious appetite, with weight gain and euphoria, characteristic of other steroids, is not seen with administration of triamcinolone."

"Triamcinolone has been used for the management of a wide variety of clinical conditions usually considered amenable to systemic steroid therapy. These have included rheumatoid arthritis and other collagen diseases, allergic and dermatological disorders, certain leukemias and malignant lymphomas, the nephrotic syndrome, pulmonary emphysema and fibrosis, acute bursitis, rheumatic fever, and certain blood dyscrasias. Although clinical experience with the drug in some of the foregoing conditions is not extensive, the many similarities in action between triamcinolone and other potent glucocorticoids would indicate a usefulness for triamcinolone akin to that of other agents of this class."

"There is some evidence that triamcinolone is more effective at a smaller dosage than are other steroids in controlling both the skin and joint lesions in psoriasis, whether or not complicated by arthropathy."

"Triamcinolone appears to compare favorably with other steroids for use in those situations in which edema and sodium retention have been complicating problems."

"It [triamcinolone] may also be the steroid of choice for patients in whom psychic stimulation, euphoria, voracious appetite, and weight gain should be avoided."

"...the drug [triamcinolone] does produce the other side effects and untoward reactions common to the glucocorticoids. At therapeutically equivalent doses, the frequency and severity of clinical manifestations of hyperadrenalism — rounding of the face, fat deposition, and hirsutism — are essentially the same. Likewise, there is little indication that the relative incidence of osteoporosis is materially decreased after the long-term use of the drug."

"Triamcinolone apparently does not cause the euphoria sometimes seen with other steroids, and the occurrence of mental depressions is uncommon."

"Current evidence suggests that the drug [triamcinolone] may not produce as high an incidence of peptic ulcer as do other steroids."

"Cutaneous erythema seems to be a side effect peculiar to triamcinolone."

"The usual contraindications and precautions of glucocorticoid therapy should be followed in the use of triamcinolone, keeping in mind that prolonged therapy with this drug will suppress the function of the patient's own adrenals by interfering with the pituitary-adrenal axis."

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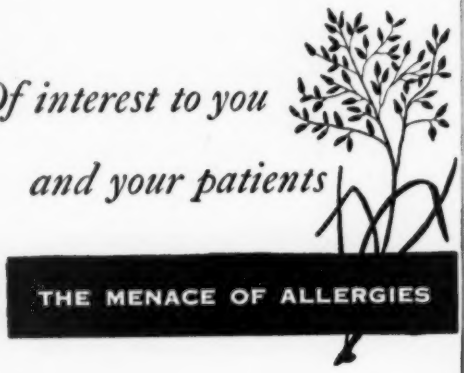

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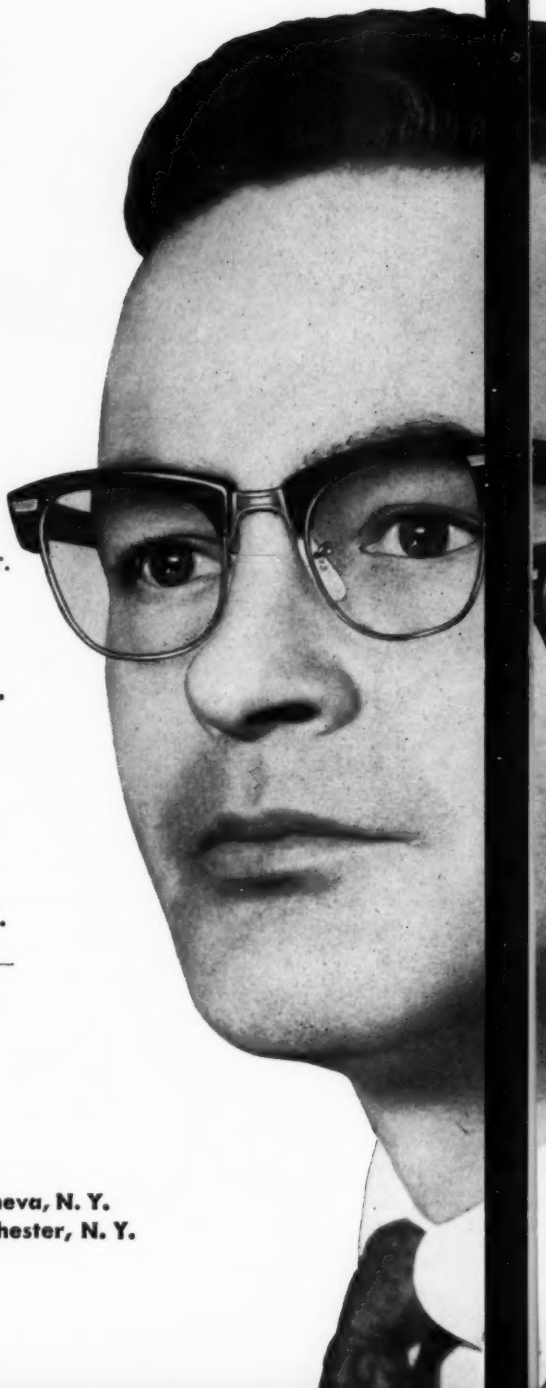

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A.M.A. ARCHIVES OF
OPHTHALMOLOGY

The Occurrence of Glaucoma Following Occlusion of the Central Retinal Artery

A Clinicopathologic Report of Six New Cases with a Review of the Literature

L. EDWARD PERRAUT, M.D., and LORENZ E. ZIMMERMAN, M.D., Washington, D. C.

During the course of routine histopathologic study of glaucomatous eyes at the Armed Forces Institute of Pathology, a number of cases have been encountered in which the glaucoma apparently followed an occlusion of the central retinal artery. That glaucoma often follows an occlusion of the central retinal vein is well known, but may glaucoma also be related pathogenetically to occlusion of the central retinal artery? This question led us to further study and finally prompted this report.

Duke-Elder,[1] in referring to the complications of occlusion of the central retinal artery, states, "secondary glaucoma has rarely occurred; in some cases it has been due to inflammatory and neovascular changes at the filtration angle, and in others it has been associated with a co-existent venous thrombosis," but he gives no additional discussion or specific references. Sommers,[2] after discussing the possible causes of glaucoma after occlusion of the central vein, states that similar causes may produce secondary glaucoma in cases of obstruction of the central retinal artery. The occurrence of glaucoma after occlusion of the central retinal artery is not mentioned by Fuchs,[3] Elwyn,[4] or Sugar[5] in their textbooks or by many others.[6-9] Between 1874 and 1930, there were 14 papers on the subject. In the literature of the two decades between 1930 and 1950, we found no case reports, but more recently several cases have been described. This literature will be reviewed later.

Upon review of cases from the Registry files, a number of possible examples of glaucoma secondary to occlusion of the central retinal artery were found, but in this report we shall confine ourselves to six of the more recent cases in which there was clinical evidence that the ocular tension did not become elevated until after arterial occlusion.

CASE 1.—A 60-year-old white man stated that on Aug. 8, 1954, he developed an acute upper respiratory infection for which he was given sulfonamides. This was followed by swelling of the eyelids and face. On Aug. 10, the patient noted the sudden complete loss of vision in his left eye. He was hospitalized on Sept. 2, because of severe dyspnea. Diagnoses at this time were acute congestive heart failure secondary to arteriosclerotic heart disease, diabetes mellitus, Laennec's cirrhosis, and esophageal varices. The patient was first seen by an

Submitted for publication Dec. 13, 1958.

From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology.

Resident in Ophthalmology, Washington Hospital Center (Dr. Perraut), and Chief, Ophthalmic Pathology Branch, Armed Forces Institute of Pathology (Dr. Zimmerman).

ophthalmologist on Sept. 10 (one month after loss of vision). Corrected visual acuity was 20/60 in the right eye, but there was no light perception in the left eye. Both eyes were normal to external examination. The pupils were round, regular, and equal. The right pupil reacted well directly to light but not consensually. The left pupil reacted consensually but not directly to light. Intraocular pressure measured 20 mm. Hg (Schiøtz) in both eyes. Ophthalmoscopy revealed the right disc to have a normal pale yellow color. There was moderate arteriolar attenuation with yellow light reflex. The A/V ratio was 1:3, and there was moderate nicking. There were no exudates, and the macula was normal. The left disc was round and pale white. The rest of the fundus presented a classical picture of central retinal arterial occlusion. The arterioles were almost completely obliterated, appearing as small white streaks partially filled with blood in some places. The veins were dilated, irregular, and markedly compressed by the arterioles. The retina was opaque and milky-white, particularly in the macular area, causing the fovea to stand out as a bright red spot. The patient was treated with papaverine and nicotinic acid without any improvement of vision. On Sept. 26 (46 days after the onset of visual loss), the patient complained of pain in the left eye. On Sept. 30, examination revealed no change in the right eye. The left eye, however, had a dilated fixed pupil, and there was mild injection of the bulbar conjunctiva. The intraocular tension was 53 mm. Hg in the left eye; 16.9 mm. Hg in the right eye. The fundus was not significantly changed. The disc was pale, the arteriolar tree was nearly obliterated, and the veins were dilated and somewhat irregular. Slit-lamp examination showed the cornea to be hazy, and no flare was seen. The iris appeared normal. A few precipitates were present on the corneal endothelium. The patient was treated with acetazolamide (Diamox), miotics, and retrobulbar injection of lidocaine (Xylocaine) on the left side. The tension remained elevated and pain continued. On Oct. 15, the left eye was enucleated. Clinical diagnosis was occlusion of the central retinal artery with secondary glaucoma. The patient died from ruptured esophageal varices three months after enucleation of the left eye. Unfortunately the right eye, which had remained unchanged, was not removed at autopsy.

Histopathologic examination of the enucleated left eye reveals the corneal epithelium to be intact. A few migratory inflammatory cells are present between the epithelium and Bowman's membrane, but

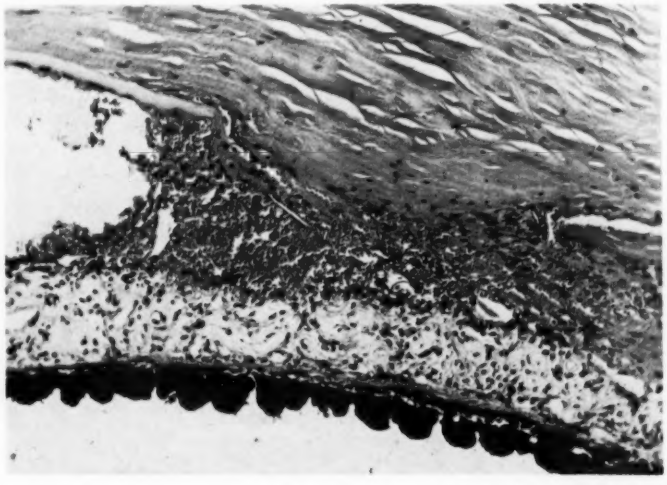


Fig. 1 (Case 1). — A small blood clot in the anterior chamber is becoming organized, and the iris has been pulled forward against the cornea. Hematoxylin and eosin; reduced about 10% from mag. × 130.

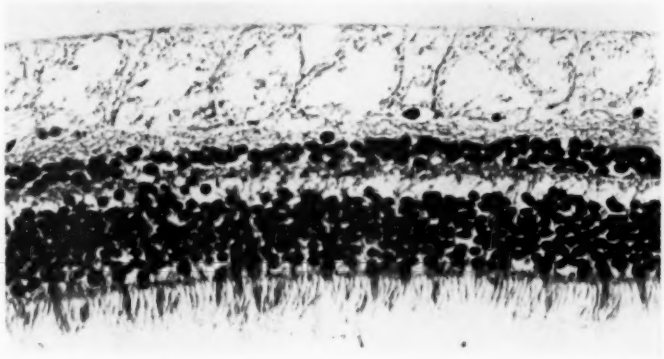


Fig. 2 (Case 1).—There is ischemic necrosis of the inner retinal layers, but the outer elements are comparatively well preserved. The very swollen disintegrating nerve fiber layer appears spongy, most of the ganglion cells have disappeared, and the inner nuclear layer is reduced to about one-fourth of its normal cell population. Hematoxylin and eosin; reduced about 10% from mag. × 400.

there is no distinct bullous keratopathy. The stroma is not significantly altered. The anterior chamber contains fresh erythrocytes, many of which are adherent to the corneal endothelium and to the anterior surface of the iris. The chamber angle on one side is obliterated by recently formed peripheral anterior synechias, while on the opposite side there is early fibrovascular organization of a small blood clot present in the angle (Fig. 1). From the organizing blood clot in the chamber angle, a thin layer of capillaries extends onto the anterior surface of the iris. Evidence of early vascularization is also present in the pupillary zone. Early ectropion uveae is observed, both the pigment epithelium and the sphincter muscle being slightly everted. Fresh blood is adherent to the anterior lens surface. Degenerative changes consisting mainly of syneresis are observed in the vitreous, but there is no hemorrhage posteriorly. The most significant changes are observed in the retina, which reveals diffuse coagulative necrosis of the nerve fiber and ganglion-cell layers. The inner nuclear layer is reduced to about one-fourth of its normal cell population. The retinal necrosis is most striking posteriorly where the disintegrating nerve fiber layer is swollen and undergoing liquefactive changes (Fig. 2). Here also some of the larger retinal arterioles are occluded by a coagulum consisting of large mononuclear cells, pyknotic nuclei of disintegrating cells, and a few proliferating endothelial cells within a fibrinous meshwork (Fig. 3). Toward the equator and at the periphery the ghostly outlines of a few vanishing ganglion cells can still be seen. There is also extensive microcystoid degeneration at the periphery. The changes characteristic of ischemic infarction are observed best in the macular region where the usually thick ganglion-cell layer has largely vanished, as have the cells of the inner nuclear layer; the per-

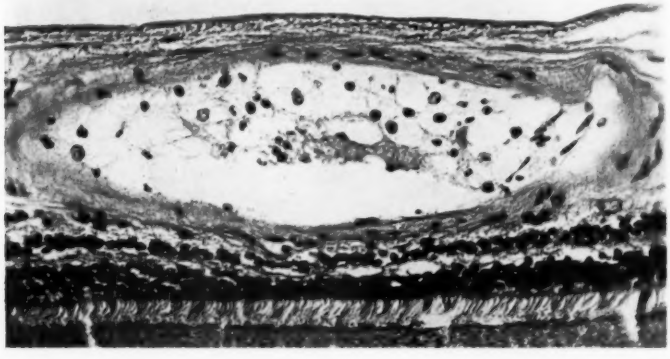


Fig. 3 (Case 1).—The lumen of a large retinal arteriole is occluded by a thrombus composed of histiocytes within a fibrinous meshwork. Hematoxylin and eosin; reduced about 10% from mag. × 300.

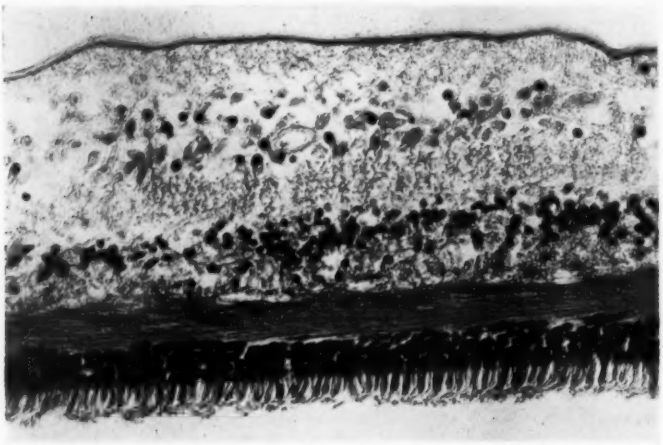


Fig. 4 (Case 1).—Ischemic infarction of the macula has produced coagulative necrosis of the ganglion cells, which can be observed at various stages of disintegration. Similar changes have taken place in the internal nuclear layer, but here the process is not as far advanced, presumably because this layer receives a greater diffusion of oxygen from the choroid than does the ganglion-cell layer. Hematoxylin and eosin; reduced about 10% from mag. × 300.

cipient elements and their nuclei, on the other hand, remain comparatively well preserved (Fig. 4). The optic nerve head reveals extensive degeneration of nerve fibers and diffuse glial proliferation. Gross cupping is not present. Transverse sections of the optic nerve taken at the level of the lamina cribrosa reveal the central retinal artery to have a large lumen completely plugged by an acellular, amorphous mass which is largely calcified (Fig. 5). The mass extends over a distance of more than 25 serial sections (at least 150μ). The vessel wall shows marked fibrous thickening of all coats. Cellular proliferation is negligible, and the tissue appears markedly sclerotic. No atheromatous deposits are seen in the plane of section, and there is only minimal thickening of the intima. The internal elastic lamina is thickened and prominent.

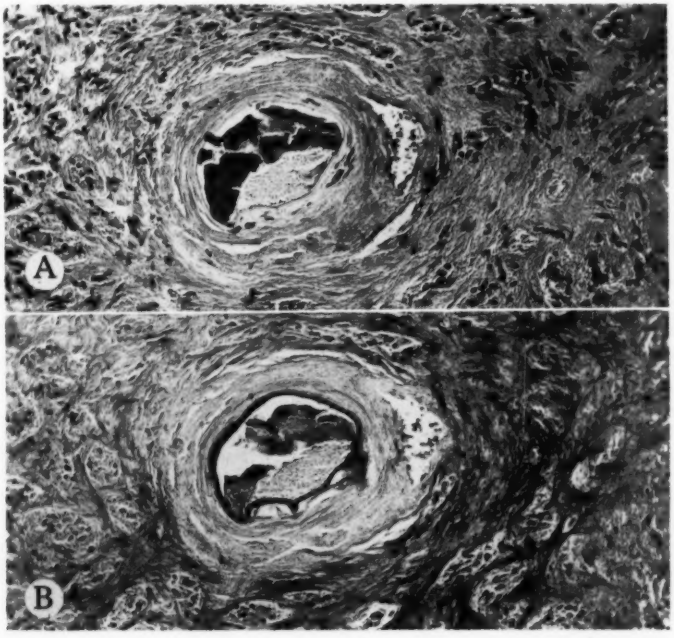


Fig. 5 (Case 1).—The central retinal artery is occluded by a largely calcified acellular thrombus. *A*, hematoxylin and eosin; *B*, Verhoeff's elastic tissue stain; both reduced about 10% from mag. × 130.

The acellular mass which occludes the lumen appears to rest directly on the internal elastic lamina, and no endothelial cells can be identified with certainty. Immediately posterior to the site of arterial occlusion, the vessel wall becomes contracted and the lumen obliterated by the extreme degree of medial contraction.

CASE 2.—A 70-year-old white man gave a history of sudden loss of vision in his right eye on Oct. 24, 1949. Six days later ophthalmoscopic examination of the right eye revealed evidence of an occlusion of the central retinal artery. The only abnormality noted in the other eye was moderate angiosclerosis. Tonometry was not done at this time, but tactile tension was normal bilaterally. The patient was diabetic, and he had required 40 units of insulin daily. His blood pressure was 210/100. He was treated with vasodilators, but no improvement in vision occurred. On Dec. 2 (39 days after the sudden loss of vision), the patient began having pain in his right eye. The intraocular tension of the right eye, taken on Dec. 5, was 80 mm. Hg (Schiøtz). Pain in the right eye continued despite treatment of the glaucoma, and the eye was enucleated on Dec. 15, 1949. The clinical diagnosis was occlusion of the central retinal artery followed by glaucoma. When the patient was last seen, on Dec. 23, 1949, the tension in the left eye was normal; he died of a coronary occlusion shortly thereafter. Autopsy was not performed.

Microscopic examination of the enucleated right eye reveals moderate edema of the basal-cell layer of the corneal epithelium and early pannus formation at the far periphery. The anterior chamber is shallow but free of gross hemorrhage or exudate. On the temporal side the anterior chamber angle is essentially open, though the root of the iris is angulated forward and adherent to the face of the ciliary body (Fig. 6). The uveal tissues in this area are lightly infiltrated by erythrocytes, lymphocytes, and plasma cells, and there is early proliferation of mesenchymal cells which form a bridge between the iris root and the most posterior portion of the corneoscleral trabecula. Most of the trabecula on this side is completely open to the anterior chamber. There is, however, a conspicuous, though delicate plaque of hypertrophic endothelial cells which have proliferated over the inner

Fig. 6 (Case 2).—The anterior chamber angle is still open, though the iris root has already become adherent to the face of the ciliary body. A very delicate layer of endothelial cells extends from the iris root onto the inner surface of the trabecula (arrows). Hematoxylin and eosin; × 50.

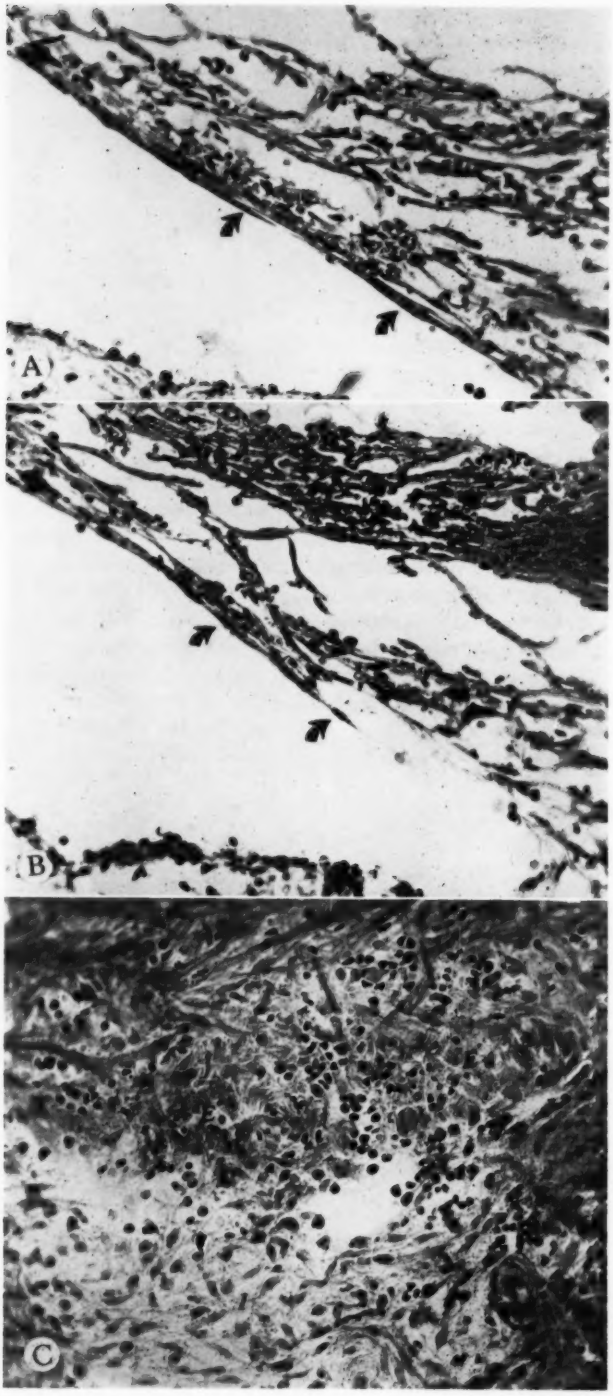


Fig. 7 (Case 2).—The thin membrane composed of elongated spindle cells (arrows) which covers the inner surface of the trabecula is shown by meridional sections in *A* and *B*. The same cells seen as an endothelial sheet are demonstrated (at *E*) by tangential section in *C*. The trabecular fibers are shown at the top of the field and the anterior iris stroma below (*I*). *A* and *B* reduced about 10% from mag. × 305. *C* reduced about 10% from mag. × 265.

surface of the trabecula. These can be seen both in meridional and in tangential sections (Fig. 7).* Red blood cells and a few mononuclear leukocytes are seen within the intertrabecular spaces, in the stroma of the iris root, and in the ciliary body adjacent to the iris root. On the nasal side a more advanced stage of the same processes is observed. Here the iris root is adherent to the corneal endothelium up to the level of Schwalbe's line, thus covering the entire corneoscleral trabecula. Here, also, there is a proliferation of endothelial cells and capillaries along the interface between the iris and trabecula. Red blood cells are contained within the intertrabecular spaces and canal of Schlemm. Occasional small clusters of red blood cells and mononuclear inflammatory cells are present along the anterior surface of the iris. There is diffuse atrophy of the iris and focal areas of necrosis of the stroma, dilator muscle, and pigment epithelium. In the pupillary zone there is a mild proliferation of the anterior border layer of cells but no distinct neovascularization is yet evident. A number of deep-seated, thin-walled blood vessels in the iris stroma appear markedly engorged. There is no evidence of hemorrhage behind the lens. There is widespread, acute, coagulative necrosis restricted to the inner retinal layers, with sparing of the outer retinal layers. The degree of necrosis varies considerably from field to field. This is seen especially well in the macular region, where isolated clusters of seemingly viable ganglion cells still persist, while the bulk of the ganglion-cell layer reveals coagulative necrosis (Fig. 8). Similarly on the nasal side the degree of necrosis of individual ganglion cells within the same high-power field varies greatly (Fig. 9). In places there is marked edema of the nerve fiber layer, but nowhere is this as severe as that observed in Case 1. A number of vacuolated, apparently hydropic cells scattered throughout the nerve fiber and ganglion-cell layers give intensely positive staining with both the periodic acid-Schiff reaction and with Alcian blue. The retinal vessels, both arterioles and venules, are moderately engorged with blood. There is gliosis of the nerve fiber layer of the retina immediately adjacent to and in the substance of the atrophic nerve head. The large vessels on the surface of the disc reveal noteworthy thickening of their walls. The artery is packed with red blood cells, among which there are proliferating fibroblasts with long interconnecting cell processes. A large vein on the nerve head has an extremely thick, pale-staining, edematous wall but a patent lumen. A few proliferat-

* Dr. Milton Flocks furnished the tangential sections through the trabecula in Cases 2 and 4.

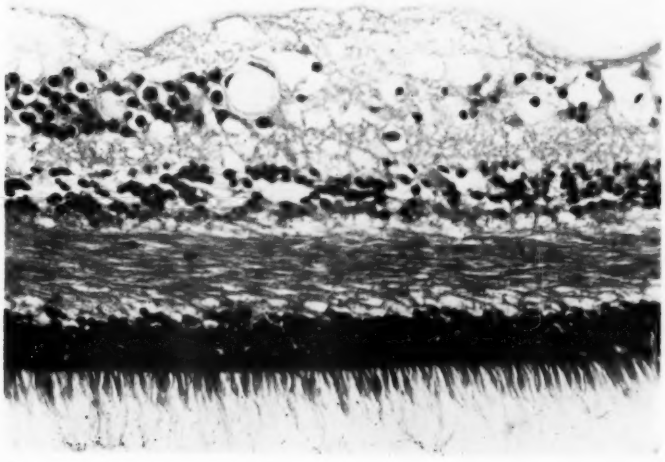


Fig. 8 (Case 2). — Severe coagulative necrosis of the inner macular layers is evident, but the damage to the ganglion cells is less advanced at the left of the field. The outer retinal layers remain very well preserved. Hematoxylin and eosin; reduced about 10% from mag. × 305.

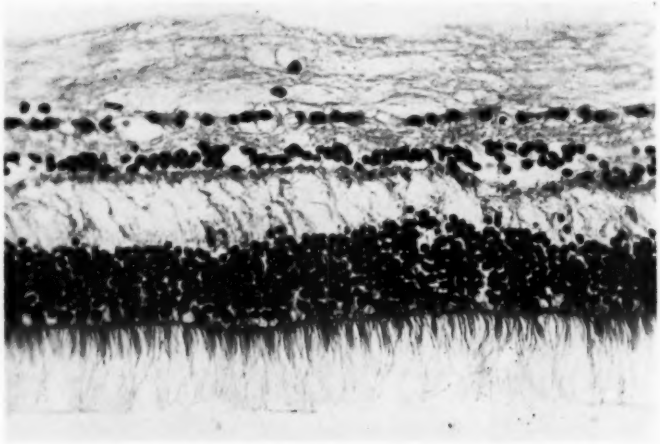


Fig. 9 (Case 2).—An area in the nasal retina shows incomplete necrosis of ganglion cells and much edematous swelling of the nerve fiber layer. The inner nuclear layer has a greatly reduced cell population, while the outer nuclear layer and the rods and cones remain very well preserved. Hematoxylin and eosin; reduced about 10% from mag. × 300.

ing capillaries are present along the surface of the disc. A cross section of the optic nerve taken immediately behind the lamina cribrosa reveals the artery to be occluded by a fresh thrombus composed of red blood cells and fibrin which is being organized by fibroblastic proliferation (Fig. 10). The adjacent vein is distended with blood, but it appears free of fibrin and fibroblastic proliferation. Its adventitia is thickened and infiltrated by lymphocytes.

CASE 3.—A 66-year-old white man complained of a sudden loss of vision in his right eye on Dec. 2, 1953. The following day he was examined by an ophthalmologist, who recorded the visual acuity as 20/20 in the left eye and no light perception in the right eye. Tension was "normal" in both eyes. Ophthalmoscopic examination revealed marked edema of the central area of the retina with a cherry-red spot in the fovea. Because the retinal arterioles did not appear very abnormal, the ophthalmologist was not certain of his diagnosis of central artery occlusion. The patient returned two weeks later, and the ophthalmoscopic findings were then definitely those of an occlusion of the central retinal artery.

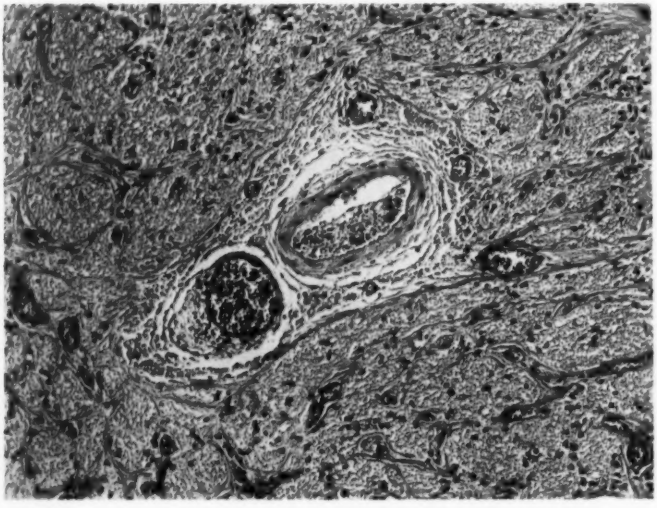


Fig. 10 (Case 2).—The central retinal artery contains a cellular thrombus which is being organized by fibroblastic proliferation. The vein is engorged with red blood cells but is not thrombosed. Both vessels have moderately thickened walls. Hematoxylin and eosin; reduced about 10% from mag. × 115.

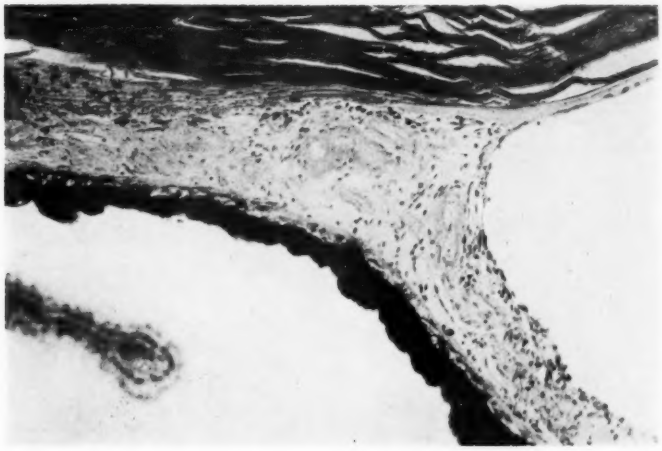


Fig. 11 (Case 3).—The anterior chamber angle is occluded by a well-developed peripheral anterior synechia. A layer of delicate capillaries extends onto the anterior surface of the atrophic iris. Hematoxylin and eosin; reduced about 10% from mag. × 145.

Tension was still "normal" in both eyes. On Jan. 20, 1954 (seven weeks after the occlusion of the central retinal artery), the right eye became red and painful and its tension had risen to 62 mm. Hg (Schiøtz). In spite of intensive miotic therapy, paracentesis, and topical hydrocortisone, the tension remained elevated. During the latter part of February, 1954, rubeosis iridis was noted and anterior synechias were also described. The eye was enucleated on May 14, 1954. The left eye has maintained a normal tension. The last examination, on March 1, 1955, revealed the tension to be 22 mm. Hg (Schiøtz), and visual acuity was 20/20.

Histopathologic examination of the enucleated right eye reveals moderate edema of the corneal epithelium. The anterior chamber angles are completely obliterated by firm, well-developed, peripheral anterior synechias (Fig. 11). A delicate layer of capillaries extends onto the anterior surface of the iris peripherally and, on one side, continues to the pupillary zone. The iris stroma is markedly atrophic and very lightly infiltrated with lymphocytes. The retina reveals a very severe degree of coagulative

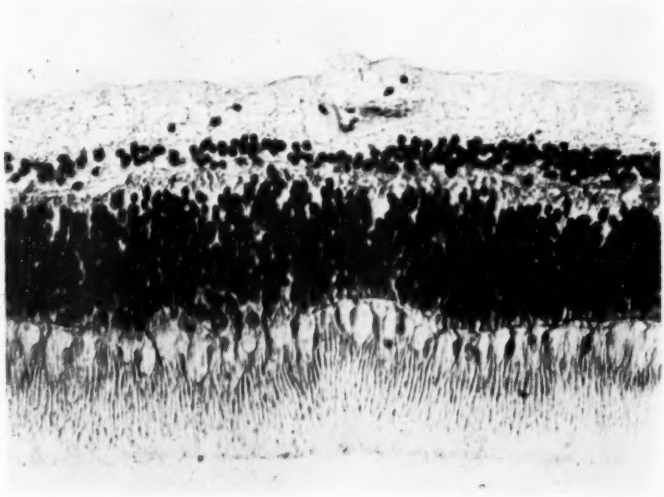


Fig. 12 (Case 3).—There is severe coagulative necrosis of the inner retinal layers. Ganglion cells have disappeared, and the inner nuclear layer is much reduced in thickness. Hematoxylin and eosin; reduced about 10% from mag. × 350.

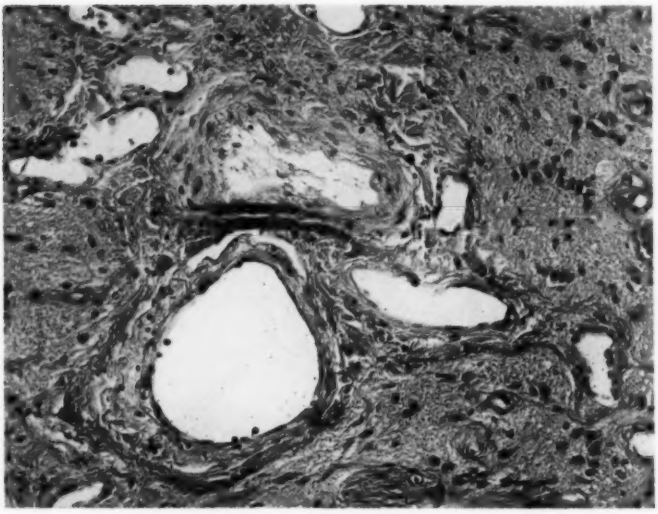


Fig. 13 (Case 3).—The central retinal artery (near top of field) is obliterated by a pale-staining fibrous thrombus, while the central vein is widely patent. Hematoxylin and eosin; reduced about 10% from mag. × 115.

necrosis involving only the inner layers (Fig. 12). Remnants of only occasional ganglion cells can be found. Scattered pyknotic nuclei are present in the ganglion-cell layer. The internal nuclear layer is reduced to one to three cells in thickness. Moderate edema is observed in the external plexiform layer posteriorly. There is marked gliosis in the retina about the deeply cupped optic disc. The optic nerve is markedly atrophic. The retinal blood vessels are all collapsed and their lumens obliterated. A cross section of the optic nerve approximately 2 mm. posterior to the lamina cribrosa reveals the central retinal artery to be partially collapsed and to have its lumen obliterated by proliferated fibroblasts (Fig. 13). No red blood cells remain in the lumen. The central retinal vein has a large dilated empty lumen; its wall is moderately thickened and very lightly infiltrated by lymphocytes.

Case 4.—A 69-year-old white man gave a history of a sudden loss of vision in his right eye on March 15, 1950. At that time

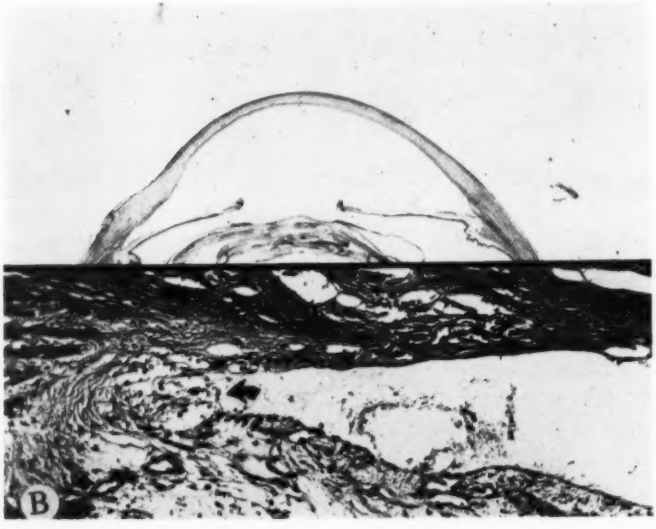


Fig. 14 (Case 4).—A (upper portion of cut), the anterior chamber is deep, and the angle is open on each side. *B*, there is a small amount of fibrinocellular exudate in the chamber angle. At the extreme periphery a proliferation of mesenchymal cells from the iris root into the anterior chamber is indicated by the arrow. Hematoxylin and eosin; *A*, reduced about 10% from mag. × 4; *B*, reduced about 10% from mag. × 115.

ophthalmoscopic examination showed some retinal hemorrhages and exudates. Tension was normal with the Schiøtz tonometer. A clinical diagnosis of occlusion of the central retinal artery was made on May 1, 1950. The patient was known to have had hypertension. On May 6 (52 days after the onset of visual loss), the tension of the right eye rose to 90 mm. Hg (Schiøtz), and this eye was enucleated because of severe pain. We have been unable to obtain follow-up information as to the condition of the remaining eye.

Sections prepared from the enucleated right eye reveal an intact corneal epithelium with early pannus formation at the periphery. The anterior chamber is deep, and most of the chamber angle is open (Fig. 14). A small amount of fibrinocellular exudate is present in the anterior chamber angles on both sides. A few red and white blood cells are scattered in the anterior chamber angle and in the trabecula. In many sections there are mesenchymal cells which have proliferated from the iris root into the anterior chamber (Fig. 14*B*). This generally involves only the area adjacent to the scleral spur. In occasional sections, however, the chamber angle on one side is obliterated by synechiae, which cover almost all of the trabecular area. The corneoscleral trabeculae appear thickened, and the intertrabecular spaces are compressed. The canal of Schlemm, however, is patent. Even in the areas where the trabecula is freely exposed to the anterior chamber, a thick, prominent layer of endothelium which can be seen in meridional as well as tangential sections has developed over the inner surface of the trabecula. The iris is extremely atrophic and lightly infiltrated by chronic inflammatory cells. Early rubeosis is observed in the pupillary zone as well as at the iris root. The pupillary region of the iris is especially atrophic, and early ectropion uveae involving the sphincter muscle as well as the pigment epithelium is evident. There is no significant hemorrhage posteriorly. The retina shows widespread degeneration of the inner layers and relative preservation of the outer (Fig. 15). Coagulative necrosis of focal groups of ganglion cells and nuclei in the inner nuclear layer is seen throughout all portions of the retina. Mild edema is present in the nerve fiber layer, and there is gliosis in the peripapillary region. The nerve head itself also shows marked glial proliferation. The central retinal artery, seen in longitudinal section as it passes through the lamina cribrosa into the nerve head, is completely occluded by a highly cellular fibrous plaque which fills the lumen (Fig. 16).

CASE 5.—A 54-year-old white man who had had symptoms of Buerger's disease for three years was hospitalized Aug. 1,

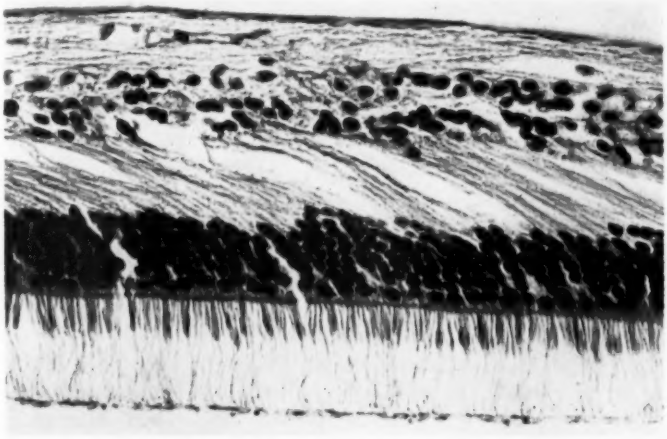


Fig. 15 (Case 4).—Retinal infarction has led to a disappearance of ganglion cells and to severe degeneration of the inner nuclear layer. The rods and cones and their nuclei are unaffected. Hematoxylin and eosin; reduced about 10% from mag. × 400.

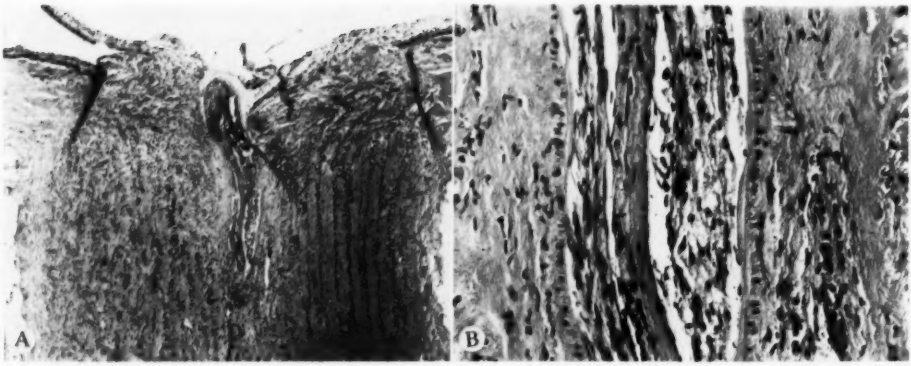


Fig. 16 (Case 4).—The central retinal artery is occluded by a large organized thrombus. *A*, reduced 35% from mag. × 50; *B*, reduced 35% from mag. × 305.

1956, in order to have bilateral sympathectomies. Visual acuity was 20/20 in the right eye and 20/25 in the left eye. Both pupils reacted to light normally. Funduscopic examination showed no abnormalities in either eye. The patient's blood pressure ranged from 140/90 to 180/100 during hospitalization. There was discoloration of the second and fifth toes of the right foot. Bilateral lumbar sympathectomies were done, and the patient was discharged on Oct. 3, 1956. Sudden complete loss of vision in the left eye occurred on Oct. 15. Examination revealed evidence of occlusion of the central retinal artery of the left eye. The patient was treated with vasodilators, but no improvement of vision followed. On Nov. 19 (35 days after the sudden loss of vision), the patient complained of pain in the left eye, and the tension in this eye was found to be 68 mm. Hg (Schiøtz), while the tension in the right eye was 20 mm. Hg. There was no light perception in the left eye, but visual acuity was 20/20 in the right eye. The right eye was entirely normal. The left eye showed circumcorneal injection, epithelial edema of the cornea, dilated vessels near the pupillary border of the iris, and posterior synechia from 10 to 5 o'clock. The anterior chamber was of normal depth, and no flare or cells were seen. Pilocarpine, eserine, and retrobulbar injection of procaine had almost no effect on the tension of this left eye. On Nov. 23, a posterior sclerotomy was done which also did not lower the tension. Because of continued pain and elevated tension, the left eye was enucleated on Nov. 26, 1956.

Microscopic examination of the enucleated left eye reveals mild corneal edema. Only a small amount of serous exudate is present in the shallow anterior chamber. Well-developed peripheral anterior synechiae completely seal over the trabecular area on one side and almost completely on the other. The intertrabecular spaces are largely obliterated, and the corneoscleral trabeculae appear thickened. The canal of Schlemm contains red blood cells on both sides. Except at the root of the iris where the iris stroma is angulated forward against the trabecula, the remainder of the iris diaphragm is displaced forward only slightly. The iris stroma shows moderate atrophy. A network of capillaries covers the anterior surface of the iris in the pupillary zone, but there is no significant ectropion. No significant hemorrhage is evident in either the anterior or the posterior segment. There is diffuse coagulative necrosis involving the inner retinal layers but sparing the outer layers. The ganglion cells which have not completely vanished can be identified in varying stages of disintegration, some appearing only as ghostly outlines (Fig. 17). Many of the retinal blood vessels are still engorged with viable erythrocytes; others, however, are filled with

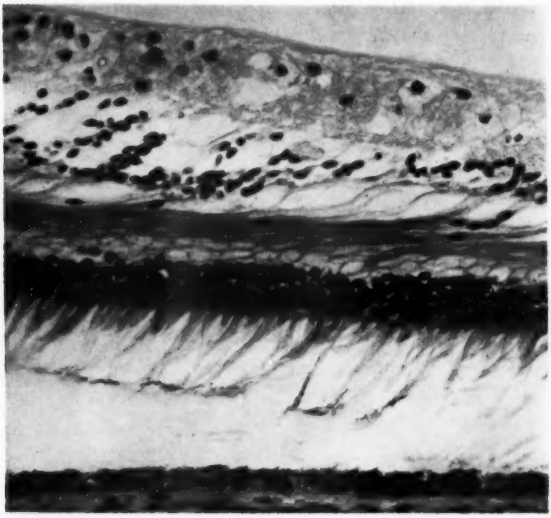


Fig. 17 (Case 5).—There is ischemic necrosis of the inner retinal layers. Hematoxylin and eosin; ×305.

amorphous, pale, granular material of uncertain composition. Most of the vessels peripheral to the equator contain this type of material, while some vessels located posterior to the equator contain mixtures of viable erythrocytes and granular material. A number of the arterioles with greatly thickened walls present no discernible lumens. There is marked gliosis in the nerve fiber layer of the peripapillary region, and the optic disc itself shows widespread glial proliferation (Fig. 18). The vessels present in the disc have greatly thickened walls. One major artery on the nasal edge of the disc contains a recanalized thrombus. Cross sections of the optic nerve taken posterior to the lamina cribrosa reveal the central retinal artery to have a collapsed wall, with its very small lumen completely replaced by a fibrous thrombus containing many pyknotic nuclei but no remaining erythrocytes (Fig. 19).

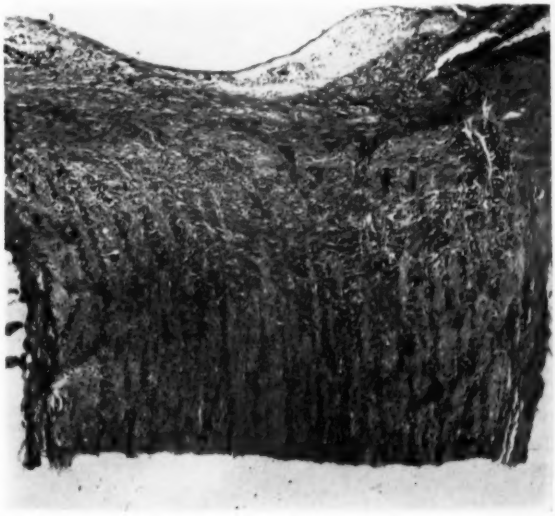


Fig. 18 (Case 5).—Markedly sclerotic vessels are seen on the surface of the atrophic nerve head. Hematoxylin and eosin; ×50.

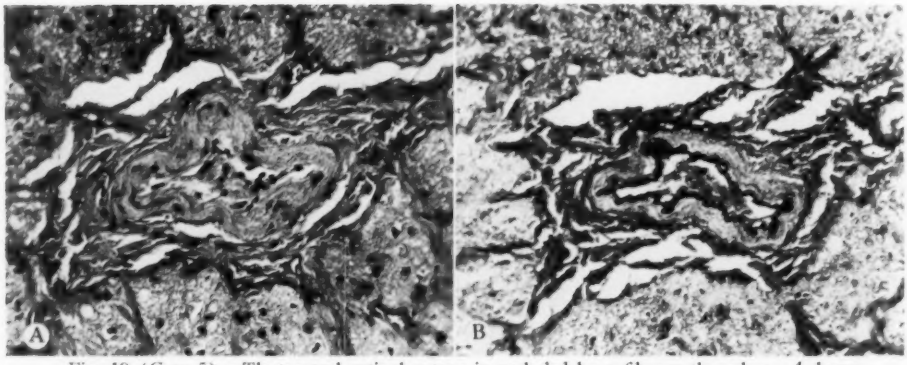
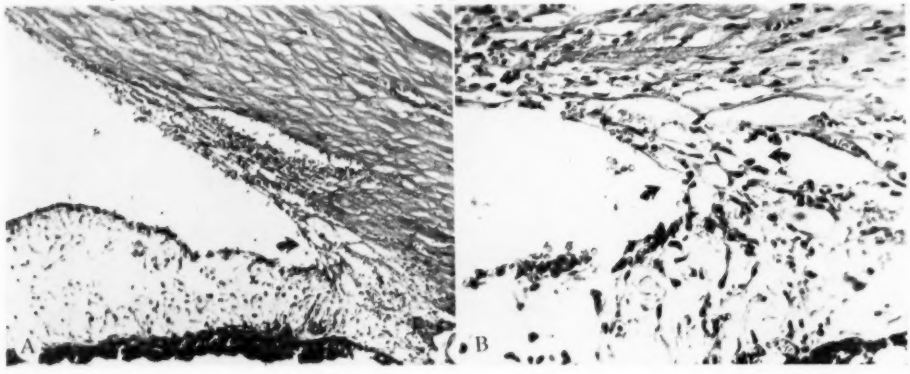


Fig. 19 (Case 5).—The central retinal artery is occluded by a fibrous thrombus. *A*, hematoxylin and eosin; *B*, elastic tissue stain; both reduced 35% from mag. × 305.

CASE 6.—A 74-year-old white man, a diabetic of 15 years' duration, was examined on April 19, 1958, five hours after the sudden loss of vision in his right eye. The right eye had no light perception, while the visual acuity of the left eye was correctable to 20/50. Funduscopic examination revealed no retinopathy and no papilledema, but the arterioles in the right eye were very tiny and the macula contained a cherry-red spot. A diagnosis of occlusion of the right central retinal artery was made. The tension at that time was normal in both eyes. General physical examination revealed evidence of advanced arteriosclerosis. The blood pressure was 220/140 and a fasting blood sugar 190 mg. %. Although no vision returned in the right eye, it was otherwise asymptomatic until May 28, when it became very painful. Examination on May 29 revealed the intraocular pressure to have risen to 60 mm. Hg (Schiøtz) in the right eye. The left eye has remained normotensive. The right optic disc appeared edematous. Miotics did not lower the pressure or relieve the pain. Enucleation of the right eye was performed on June 8, 1958, seven weeks after the sudden onset of visual loss.

Microscopic examination of the enucleated right eye reveals partial denudation of the corneal epithelium and a hyalinized pannus at the periphery. Endothelial cells and fine capillaries have grown out from the iris root, traversed the anterior chamber angle, and extended onto the inner surface of the trabecula (Fig. 20). Early peripheral

Fig. 20 (Case 6).—An outgrowth of mesenchymal cells from the anterior surface of the iris (arrows) traverses the anterior chamber angle and continues forward along the inner surface of the trabecula. *A*, hematoxylin and eosin; reduced 35% from mag. × 115. *B*, hematoxylin and eosin; reduced 35% from mag. × 305.



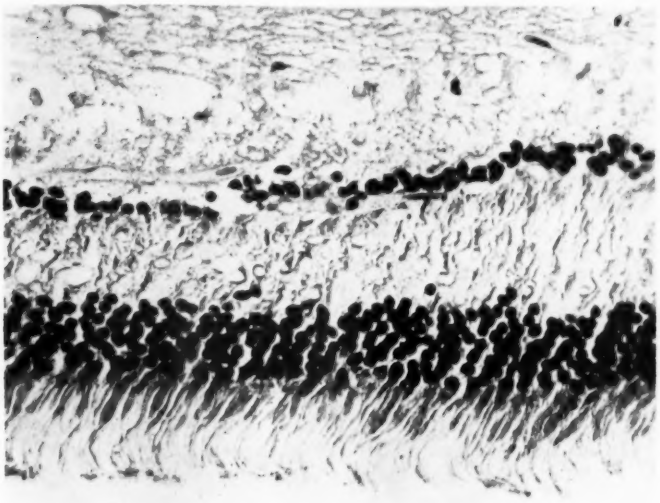
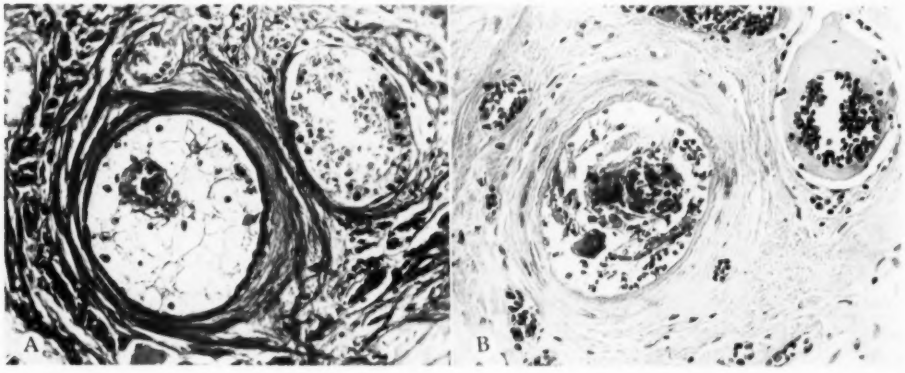


Fig. 21 (Case 6).—Ischemic infarction has produced marked edema of the inner retinal layers, disappearance of most of the ganglion cells, and a marked reduction in the number of nuclei in the inner nuclear layer. Hematoxylin and eosin; reduced about 10% from mag. × 450.

synechiae have formed in places. Engorged capillaries and a few free red blood cells are present in the iris root, chamber angle, trabecula, and canal of Schlemm. Minute foci of acute ischemic necrosis are seen in the iris, and there is early ectropion of the pupillary margin. The retina is very edematous, especially in the nerve fiber layer where there is coagulative necrosis. There is a patchy disappearance of ganglion cells, and the cell population is reduced in the inner nuclear layer (Fig. 21). The outer retinal layers are comparatively well preserved. No retinal or vitreous hemorrhages are observed. There is no excavation of the nerve head and no bowing of the lamina cribrosa. Transverse sections of the optic nerve reveal an extensive area of severe atheromatosis in the central retinal artery. The intima is greatly thickened by a massive infiltration of large foamy macrophages, and the lumen is virtually obliterated (Fig. 22*A*). In one area hemorrhage has occurred within the atheroma, and here the lumen is obliterated (Fig. 22*B*).

Fig. 22 (Case 6).—*A*, there is great narrowing of the lumen of the central retinal artery as a result of the accumulation of large foamy histiocytes between the internal elastic lamina and the endothelium. Elastic tissue stain; reduced 35% from mag. × 305. *B*, hemorrhage into the atheromatous intima has led to occlusion of the central retinal artery. Hematoxylin and eosin; reduced 35% from mag. × 305.



Cases of Occlusion of the Central Retinal Artery Followed by Glaucoma

Author	Age	Sex	Associated Clinical Features	Time Between Central Retinal Artery Occlusion & Glaucoma	Time Between Central Retinal Artery Occlusion & Enucleation	Pathologic Confirmation
Loring[14]	62	F	Good health	8 wk.	4 mo.	?
Nettleship[15]	54	M	Aortic and mitral bruit	3 mo.	4 mo.	?
Watson & Nettleship[16]	62	F	Cardiac murmur	9 ½ wk.	6 mo.	Yes
Knapp[17]	?		Diabetes mellitus with retinopathy	5 wk.	Date of enucleation not stated	No
Manz[18]	65	F	Cardiac enlargement	10 mo.	Autopsy 1 yr. after occlusion	Yes
Marple[19]	56	F	Cardiac disease	5-7 wk.	7 wk.	Yes
Ridley[20]	57	M	Cardiac arrhythmia	8 ½ wk.	3 mo.	No
Galinowsky[21]	74	F	Cardiac enlargement	6-7 wk.	2 ½ mo.	?
Harms[22] (Case 1)	48	M	Hypertrophy, left ventricle	6 wk.	5 mo.	Yes
Harms (Case 2)	57	F	Stroke 1 ½ yr. previously	4 wk.	5 mo.	Yes
Schweitzer[23]	59	M	None described	8 wk.	8 wk.	Yes
Coats[24] (Case 1)	52	F	Endocarditis; aortic regurgitation	Not given	Autopsy 3 yr. later	Yes
Coats (Case 2)	65	M	Diabetes mellitus	7 wk.	8 wk.	Yes
Coats[25] (Case 3)	71	F	Mitral stenosis	6 wk.	2 mo.	Yes
Opin[26]	76	M	Hypertension; mitral insufficiency	4 wk.	1 ½ mo.	Yes
Villard & Dejean[27]	71	F	Hypertension	8 ½ wk.	3 mo.	?
Bussola[28]	54	M	Hypertension; mitral insufficiency	7 wk.	2 mo.	Yes
Ross[10]	72	M	Hypertension	O. S.-4 mo. O. D.-8 ½ wk.	Not enucleated	No
Holt[29]	57	M	Intermittent claudication	5 wk.	Not enucleated	No
Benton[11] (Case 1)	73	F	Hypertension; diabetes mellitus	10 ½ wk.	11 wk.	Yes
Benton (Case 2)	49	?	Hypertension	6 wk.	Not enucleated	No
Winter[12]	76	F	Hypertension; diabetes	4 wk.	6 wk.	Yes
Wolter & Liddicoat[13]	84	M	Possible contusion	"Some months"	8 mo.	Yes
Wolter & Lubeck[30]	70	?		2 mo.	2 mo.	Yes
Wolter & Phillips[31]	59	M	Hypertension; cerebral vascular accident	8 ½ wk.	10 wk.	Yes
AFIP Case 1	60	M	Laennec's cirrhosis	6 ½ wk.	9 wk.	Yes
AFIP Case 2	70	M	Diabetes mellitus; hypertension	5 ½ wk.	7 ½ wk.	Yes
AFIP Case 3	66	M	None given	7 wk.	5 ½ mo.	Yes
AFIP Case 4	69	M	Hypertension	7 ½ wk.	2 mo.	Yes
AFIP Case 5	54	M	Buerger's disease; hypertension	5 wk.	6 wk.	Yes
AFIP Case 6	74	M	Diabetes & hypertension	5 ½ wk.	7 wk.	Yes

Review of the Literature

The recorded cases of glaucoma after occlusion of the central retinal artery and six more from the Registry of Ophthalmic Pathology are summarized in the Table. In each case listed there was clinical evidence of obstruction of the central retinal artery or of one of its branches. In Coats' Case 2 the superior temporal artery was obstructed; however, there was severe sclerosis of all the arterioles in the retina. The first case reported by Harms had first an occlusion of a branch; then one month later a complete occlusion of the central retinal artery.

In each case the intraocular pressure at the time of occlusion and for a while thereafter was normal as determined either by palpation or by tonometry; then a few weeks after occlusion of the central retinal artery the tension increased rather rapidly. In the majority of these cases symptoms of glaucoma appeared within nine weeks after the arterial occlusion, but there were a few exceptions. In the cases reported by Manz,[18] by Nettleship,[15] by Ross,[10] and by Wolter and Liddicoat,[13] periods of 3 to 10 months elapsed before the onset of glaucoma. In only one case was there elevation of tension in the opposite eye. This was the one reported by Ross in which glaucoma occurred bilaterally after occlusion of both central retinal arteries.[10]

In 1905, both Harms[22] and Coats[24] reviewed the literature and found eight cases

of glaucoma following occlusion of the central retinal artery. At this time Coats concluded, "The evidence therefore does not seem at present to be sufficient to decide whether there is any true causal connection between obstruction of the central artery and glaucoma. On the whole the probabilities are against it, but the decision must be left to future research." By 1913, five other cases had been reported, and Coats altered his opinion, concluding that there was good evidence that the sequence is more than coincidence and that the glaucoma is not primary in type but due to inflammation of the iris with the formation usually of a fibrovascular membrane on its surface. Leber [32] wondered if the central retinal vein was also obstructed in these cases and whether this might have produced the glaucoma, but since several of the reported cases failed to provide supporting evidence for his theory, he concluded that the glaucoma which occurred was not dependent on obstruction of the central vein. Much of what Parsons [33] had to say about glaucoma secondary to arterial occlusion is a verbatim copy from Coats' 1905 article on this subject. He added no new cases and failed to give any original discussion.

Holt's contribution was a case reported at the Chicago Ophthalmological Society; although the tension in the affected eye of her patient was not greatly elevated, there was a 12 mm. difference in pressure between the two eyes and the clinical description was otherwise very typical of the group with which we are concerned. In 1949, Benedict [34] reported 500 cases of occlusion of the central retinal vessels. There were 368 cases of occlusion of the central retinal vein and 132 of occlusion of the central retinal artery. In about 11% of the former, the vascular accident was followed by secondary glaucoma. By contrast, in only one case (less than 1%) did glaucoma occur after occlusion of the central retinal artery.

Comment

Glaucoma secondary to occlusion of the central retinal artery is a disease of the older age group. Only two patients in the collected series were not yet beyond the fifth decade, and the median age was 65. There were a few more men than women in the entire series, but the sex difference does not appear significant. The majority of these patients had some evidence of cardiovascular disease. There were six who had diabetes mellitus, and in one of our own cases the patient had undergone surgical treatment for Buerger's disease.

While the histological changes posteriorly are pathognomonic of occlusion of the central retinal artery, in the anterior segment the picture is identical with that which may be seen in the early stages of glaucoma after occlusion of the central retinal vein, before the typical rubeosis and anterior synechiae have developed. Microscopically, there are minute hemorrhages and a very few inflammatory cells in the root of the iris and in the angle of the anterior chamber. There is a proliferation of spindle-shaped mesenchymal cells and capillaries from the iris root across the anterior chamber angle and onto the trabecula. A membrane composed of delicate mesenchymal cells forms over the inner surface of the trabecula. Seen in conventional meridional sections, these cells appear as very inconspicuous slender spindle-shaped structures, but with tangential sections they are observed to form sheet-like masses of broad but flat endothelial cells. Later, varying degrees of anterior synechia and ectropion uvea are seen.

The diagnostic retinal changes which differentiate these cases from those of hemorrhagic glaucoma secondary to occlusion of the central retinal vein are as follows: There is widespread coagulative necrosis involving selectively the inner retinal layers. In those eyes enucleated early there is severe edema and great swelling of the nerve fiber layer, an incomplete disappearance of ganglion cells, a great reduction in cell population of the inner nuclear layer, and early degeneration and gliosis of the optic disc. Usually there is little or no cupping. Those

eyes enucleated later may reveal profound shrinkage of the inner retinal layers, a complete disappearance of ganglion cells, and an excavated nerve head. There is no evidence of old or recent hemorrhage in the posterior segment. Stains for hemosiderin were uniformly negative in our own cases.

In the Table there is a column designated "Pathological Confirmation," by which we mean that the findings were as follows:

1. Occlusion of the central retinal artery was demonstrated microscopically.

2. There was histopathologic evidence of ischemic infarction with its typically selective involvement of the inner retinal layers and sparing of the outer layers.

3. The retina showed no evidence of primary venous occlusion.

4. There was no evidence of any other etiological factor which might have produced the glaucoma.

We do not believe that secondary occlusive changes in the central retinal vein observed along with the arterial thrombosis in certain cases requires deletion of the case, providing that there was neither clinical nor pathologic evidence that the venous occlusion was primary. In our own cases venous thrombosis was not found, but in two cases the central retinal vein was collapsed. Certainly the retinal picture, both clinically and pathologically, was remarkably different from that characteristic of primary occlusion of the central retinal vein—even in those cases reported as having shown evidence of secondary obstructive endophlebitis.

In a number of the published reports, "pathologic confirmation" was lacking, either because enucleation was not performed or because the histopathologic changes as reported were not completely characteristic.

In four cases the question might be raised as to whether mydriatics may have precipitated an angle-closure glaucoma. Nettleship's patient received atropine after occlusion of the central retinal artery, but glaucoma did not occur until three months later; glaucoma did not occur until two weeks after atropine was used in Galinowsky's patient. In Ridley's case, 1% homatropine was used to dilate the pupil for better fundus visualization and then eserine was instilled into the eye. Four days later the patient returned with glaucoma, but whether the mydriatic produced the glaucoma or not, we cannot say.

In Coats' Case 1 an iridectomy and a cataract extraction had been done and then after a needling procedure, occlusion of the central retinal artery occurred. It is possible that the glaucoma was due to other causes in this case.

Just as treatment of glaucoma after central venous occlusion is notoriously unsuccessful, so is this true of glaucoma which follows occlusion of the central retinal artery. In nine cases some surgical procedure for glaucoma was performed, but either no effect or only a temporary lowering of intraocular pressure was obtained.

The longest follow-up of the remaining eye was reported by Opin. The remaining eye of his patient was still normal five years later. In Winter's recently reported case, the remaining eye revealed no evidence of glaucoma during the two-year follow-up period.

In the two cases reported by Benton, gonioscopy revealed the angles to be open and provocative tests for glaucoma showed no abnormal rise in tension in the remaining normal eye. In a personal communication, Wolter states that glaucoma studies performed on the remaining eye of two of his cases revealed no evidence of glaucoma. Many of the patients died within a relatively short time as a result of other systemic vascular complications.

Counting our cases, there were 32 eyes affected. Symptoms of severe glaucoma were first noted within nine weeks of occlusion of the central retinal artery in three-fourths of these eyes; the median time interval was seven weeks. Twenty-five of the eyes were enucleated surgically, and of these nineteen came to enucleation within a month of the onset of symptoms of glaucoma. In the Armed Forces Institute of Pathology cases enucleation was performed

within 19 days of the onset of pain in five of the six cases.

In the majority of cases glaucoma occurred between five and nine weeks after central retinal artery occlusion. This is an important observation, for the time interval is evidently much shorter than that which is characteristic for the glaucoma which follows occlusion of the central retinal vein. The time required for the development of glaucoma after occlusion of the central retinal vein is said to be about three months.[5]

The pathogenesis of glaucoma after occlusion of the central retinal artery is no better understood than is the glaucoma which follows occlusion of the central retinal vein. The pathologic picture in the anterior segment of the eye in the two situations is very similar, both in early and in late cases. Leber thought that these anterior segment changes were due to toxic products from the degenerating retina being carried to the filtration angle and to the iris where the resorption of intraocular fluids takes place.

In Opin's case an examination of the remaining eye five years after enucleation of the glaucomatous eye revealed no evidence of any retinal arteriosclerosis. He concluded that the obstruction of the central artery in the enucleated eye was not dependent on some preexisting vascular lesions, as some authors have postulated. He also believed as Leber did that the necrosis of the retina produced a toxin which was carried by the intraocular fluids into the anterior chamber angle.

In four of our own cases the eyes were enucleated before well-developed peripheral anterior synechiae had formed. Each of these eyes revealed evidence of microhemorrhage in the anterior chamber angles. Each also revealed a proliferation of mesenchymal cells and minute blood vessels arising from the uveal tissues of the iris root and face of the ciliary body. Associated with this was the formation of an obstructing sheet of mesenchymal cells along the inner surface of the trabecula. Thus it would seem that the rise in intraocular pressure did not develop as a consequence of advanced peripheral anterior synechia but more likely as a result of the formation of a membrane covering the ordinarily large openings through which aqueous passes from the anterior chamber into the trabecula.

The frequency with which glaucoma follows occlusion of the central retinal artery is impossible to determine. We personally share the opinion expressed by Wolter and others that the condition is not nearly so rare as generally believed. We have studied a number of other cases in the Registry files which were not included in this report for lack of pertinent clinical data. In reviewing the literature and in going over cases in the Registry we found it extremely difficult to establish criteria for acceptability. If one really wants to be hypercritical and set up very stringent criteria, we would have to conclude that a completely acceptable case is yet to be reported. Such a case should have had a modern glaucoma work-up, including tonography and provocative tests on each eye before the actual occlusion, soon after the arterial occlusion and, finally, after the onset of pain. It is not likely that many cases meeting such rigid requirements will ever be reported. For our own purposes we have accepted those cases in which examination during the interval between arterial occlusion and onset of ocular pain revealed normal tension in both eyes. We have had to discard several pathologically acceptable cases because the ocular tension prior to the onset of ocular pain was unknown. Attempts have been made to obtain the results of a really complete study of the remaining eye in the six cases reported here, but for a variety of reasons this has not been accomplished.

Summary

A clinicopathologic study of six cases of glaucoma after occlusion of the central retinal artery has been made. These cases together with our review of the literature has led us to the conclusion that glaucoma after occlusion of the central retinal artery is a distinct clinicopathologic entity, albeit

a much less common one than glaucoma after occlusion of the central retinal vein. Typically there is an abrupt onset of ocular pain due to secondary glaucoma within nine weeks of the time of arterial occlusion. Treatment of this secondary glaucoma is generally unsuccessful, and the eye is frequently enucleated soon after the onset of ocular pain.

The pathogenesis of the glaucoma in these cases, like that which follows occlusion of the central retinal vein, is not understood. Histopathologic study in early cases before the formation of well-developed anterior synechiae has provided evidence that something provokes an outgrowth of mesenchymal cells from the uveal tissues of the iris root. These cells invade the chamber angle to form a delicate membrane along the inner surface of the trabecula. It is this newly formed tissue which is believed to cause the initial obstruction to the outflow of aqueous. Subsequently, the formation of broad peripheral anterior synechiae aggravates the obstruction.

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Adie's Syndrome

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I. Response of Iris Sphincter and Ciliary Muscle to Greatly Diluted Solutions of Drugs

Drug tests by means of conjunctival instillation have been used in patients with pupillotonia firstly for the purpose of differential diagnosis and secondly in order to determine the site of the underlying disturbance. Whereas some drugs have, when used in the usual concentrations, no influence on the normal pupil (epinephrine, methacholine [Mecholyl]), others (cocaine, pilocarpine, eserine, etc.) are, as a rule, employed in concentrations considerably above threshold. A priori it should be possible, by making use of greatly diluted solutions of the latter drugs, to detect differences of reactivity between normal and abnormal pupils not sufficiently great to be apparent if stronger concentrations are employed. As the effect on the tonic pupil of such greatly diluted solutions has but exceptionally been investigated, it seemed a matter of interest to study the question more systematically. For this purpose the responses of the sphincter pupillae and the ciliary muscle to drugs were investigated in four patients with pupillotonia, and the reaction of the pupil was studied in three patients with syphilitic, incomplete absolute pupillary rigidity for the sake of comparison.

The size of the pupils was estimated by means of a Haab's scale in diffuse artificial light, while the patients were seated in a comfortable chair in the dark room. They were asked some time before and while the pupil sizes were taken to keep their eyes fixed on a distant point. If pupillary unrest was present, the pupils were left until they had become stationary. The same commercial make of droppers was used for all solutions. The latter were recently prepared and especial care was taken to instil solutions of methacholine immediately after they had been prepared. The patients had previously been trained not to blink at the moment when the drops were instilled.

When estimating the results, one has to take into consideration such inaccuracies as are inherent in this type of test. Conditions which govern the transport of the tear fluid toward and in the lacrimal pathways as well as conditions which influence diffusion and absorption are bound to differ from one patient to another. Likewise, the individual sensitivity to different drugs will vary from one patient to another and, in the same patient, from one examination to another. Such factors, together with varying psychological influences, will affect the results of the tests, the more so if the quantities of the drugs which are dissolved in the tear fluid are extremely small. Conclusions from the results can, therefore, be more readily drawn in those cases where uniocular involvement makes it possible to compare the affected eye with the normal eye.

Effect of Drugs on Tonic Pupil.—T. Alajouanine and P. Morax (1938), who studied the effect on the tonic pupil of cocaine, eserine, pilocarpine, atropine, and homatropine in conventional concentrations, stated that it reacted more quickly and more extensively to all these drugs than does the normal pupil. There appears to exist, in the literature, a good deal of disagreement as to the validity of this statement as a whole.

To quote but a few opinions, G. S. Graveson (1949) obtained "normal" responses with both eserine and homatropine and W. Kyrieleis (1951), who commands

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a particularly great personal experience in the matter, while confirming that cocaine and pilocarpine act with great regularity more rapidly and more extensively on the tonic than on the normal pupil, holds the reverse to be true as regards homatropine. H. G. Scheie (1940), on the other hand, found both the normal and the tonic pupil to dilate equally well with cocaine and homatropine and to contract equally well with pilocarpine and eserine. When making use, however, of a solution of physostigmine salycilate as dilute as 0.004%, H. G. Scheie and F. H. Adler (1940) obtained constriction of the tonic pupil, whereas no contraction occurred in the normal pupil. Besides, the tonic pupil contracted with 0.25% eserine much more quickly than the normal pupil. D. Cogan (1940), on the contrary, who also used a greatly diluted solution of physostigmine (0.008%) observed an equal response of both the normal and the tonic pupil. In a case of Scheie's, a solution of prostigmine 1:2,500 left both the normal and the tonic pupil unaltered.

A particularly important contribution was made by Scheie and Adler by their finding of the marked miotic effect on the tonic pupil of a 2.5% solution of acetyl-β-methylcholine (Mecholyl). The same concentration had no influence on the unaffected pupils or on those of normal controls. This observation has, with but a few exceptions, been confirmed by later observers (A. Franceschetti and V. Bischler, W. Kyrieleis, and others), the "methacholine test" having come to be considered a diagnostical means for differentiating the tonic pupil from other pupillary disorders. Only a minority of observers has been unable unconditionally to confirm Scheie and Adler's observation, among whom is Graveson, who, making use of a 2.5% solution of methacholine (Amechol), obtained variable results. Heuberger (1954) observed distinct miosis in but 47% and no miosis at all in 18% of his cases. According to Kyrieleis, the action of methacholine on the tonic pupil lacks absolute specificity, inasmuch as a 2.5% solution of the drug has a miotic effect, although to a much smaller degree and with less regularity, also in cases of other pupillary disorders, among which is incomplete absolute rigidity. Finally, the findings of H. Brunnschweiler (1954) should be mentioned, who, in an investigation of the effect of methacholine in 100 normal controls, observed narrowing of the pupil between 1 and 2 mm. in 14 of them.

Clinical Data on Four Patients with Pupillotonia.—All four cases, the first three of which were unilateral and the fourth bilateral, presented a characteristic picture. In the tonic pupils, whose outlines were slightly irregular, the reaction to light, direct and consensual, was absent on focal illumination. Some slight and sluggish contraction of the iris sphincter could, as a rule, be obtained on the slit lamp and a somewhat stronger reaction when a strong electric lamp was used. The reaction to light was somewhat improved by a one-hour stay in the dark room. The reaction to convergence-accommodation had a typical tonic character, the time for contraction varying between 5 and 10 seconds and the time for redilatation between 15 and 25 seconds. All tonic pupils exhibited periodic, spontaneous variations of their size in the course of each examination as well as from one examination to another. These variations were sometimes considerable. On the slit lamp, the sphincter muscle showed, in all cases, nonrhythmic, sluggish, worm-like spontaneous contractions which were often limited to one specific sector. On forcible lid closure, a tonic contraction of the affected pupil was seen in the three unilateral cases, whereas, in the pupils of the bilateral case, a slight tonic dilatation only was noted without previous constriction. No reaction to pain stimuli could be obtained in the tonic eyes, whereas the normal pupils showed a distinct dilatation to such stimuli. The general neurological examination revealed anomalies of the tendon reflexes in the first three cases only. The syphilis reactions were negative in all four cases, in both the blood serum and the cerebro-

spinal fluid, and the cell counts and chemistry in the latter were normal. The behavior of the accommodation as well as details of the clinical picture will be discussed further below.

Response of Pupils to Drugs in Pupillotonia.—The pupillary responses to various concentrations of drugs in the three unilateral cases were as follows (Fig. 1).

Sympathicomimetics: Cocaine 4% proved to have a stronger effect on the tonic than on the nontonic pupil in the two first cases, causing a greater amplitude of dilatation in Case 1, and, besides, leading up in Case 2 to a greater final pupil size. This exaggeration of the effect of cocaine was particularly evident if weaker concentrations were used (from 0.5% to 0.1%). With a 0.1% concentration the tonic pupil was dilated in Case 1 from 4.25 to 6 mm. and in Case 2 from 5 to 6 mm. after one hour, whereas in both cases the nontonic pupil did not react to these weak concentrations. Likewise, various concentrations of amphetamine (Benzedrine) and ephedrine exerted, on the whole, a definitely stronger and quicker

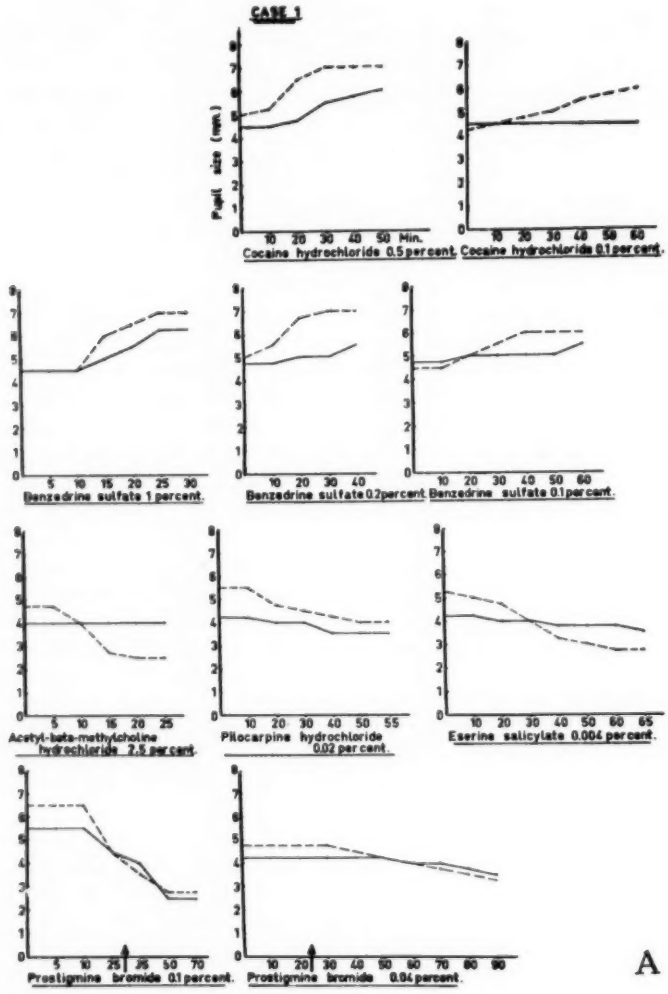
CASE 1
Pupil size (mm.)
Min.
Cocaine hydrochloride 0.5 per cent.
Cocaine hydrochloride 0.1 per cent.
Benzedrine sulfate 1 per cent.
Benzedrine sulfate 0.2 per cent.
Benzedrine sulfate 0.1 per cent.
Acetyl-beta-methylcholine hydrochloride 2.5 per cent.
Pilocarpine hydrochloride 0.02 per cent.
Eserine salicylate 0.004 per cent.
Prostigmine bromide 0.1 per cent.
Prostigmine bromide 0.04 per cent.
A

Fig. 1.—Four cases of pupillotonia. Tonic pupil on the right side in Case 2, on the left side in Cases 1 and 3; bilateral pupillotonia in Case 4. Curves showing the response of the pupils to drugs. Right pupil, solid line; left pupil, broken line. The ordinate records the pupillary sizes and the abscissa the times of reading. One drop of the respective solutions was instilled three times at five-minute intervals, except acetyl-β-methylcholine and, in Case 3, homatropine 0.25%, which were instilled only twice. The onset of refractive myopia or the increase of preexisting refractive myopia in the tonic eye is marked by an arrow. (Parts *B*, *C*, and *D* follow.)

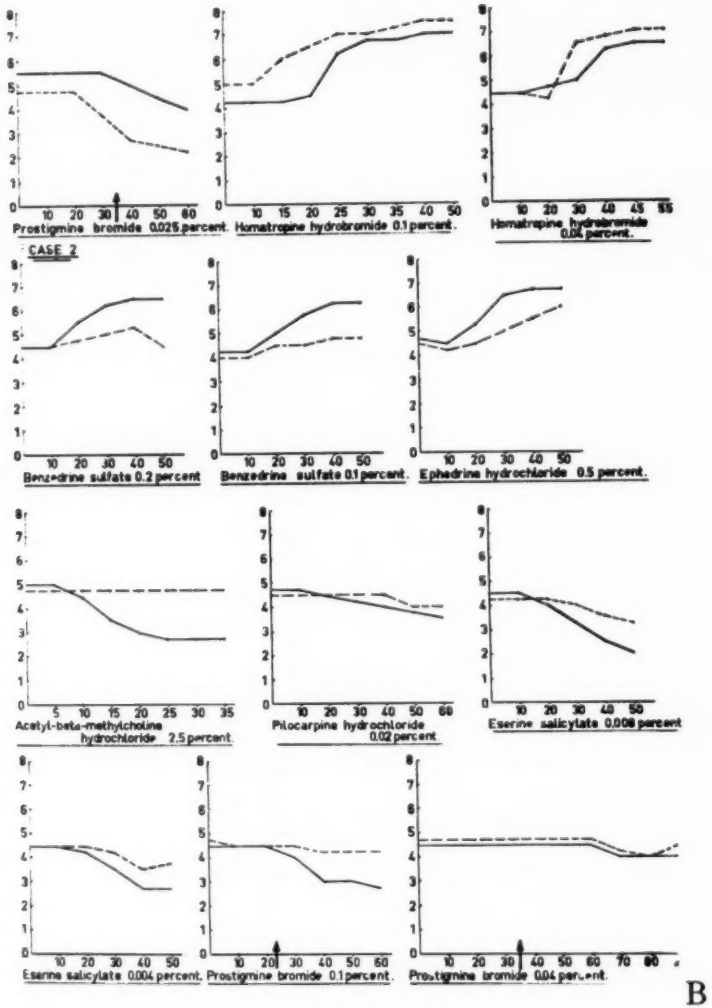

Figure 1—Continued.

mydriatic effect on the tonic pupil than on its normal fellow in the two first cases. In the third case, the influence of amphetamine was, on the contrary, somewhat stronger on the normal pupil. The usual 0.1% concentration of epinephrine caused mydriasis neither in the tonic nor in the normal eye.

Of the *parasympathicolytic drugs* only homatropine was used. In a concentration of 1% it produced bilateral maximal dilatation in the two first patients and, in a 0.25% concentration, submaximal dilatation in the third case, the final size being equal in both pupils. In Case 1, solutions of 0.1% and 0.04% also caused wide mydriasis, and the tonic pupil became slightly larger in the end. In Case 2, the tonic pupil became, with a 0.02% solution, dilated after one hour to a size 1 mm. larger than the normal pupil, the initial sizes having been equal. On the whole, the tonic pupils seemed to react somewhat more quickly to

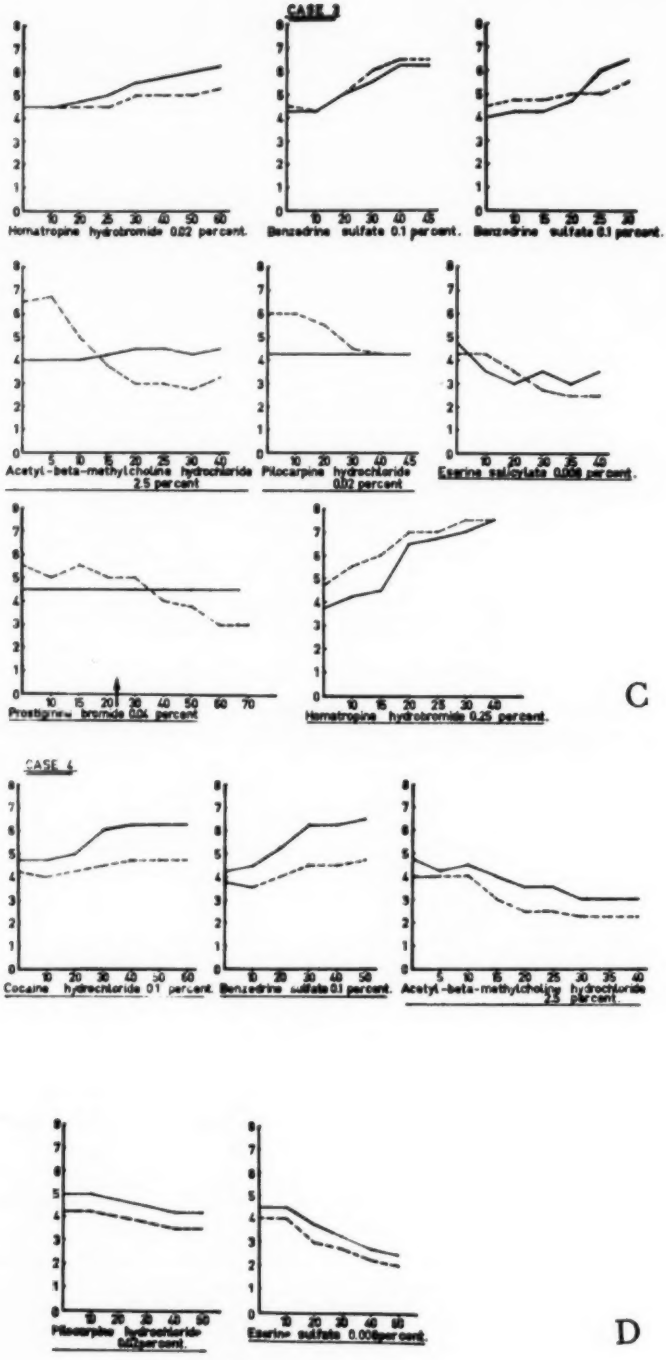

Figure 1—Continued.

low concentrations of homatropine than the normal pupils.

Parasympathicomimetics: Methacholine, 2.5%, produced, in agreement with the majority of observations in the literature, rapid and marked miosis of the tonic pupil in all three cases, whereas it failed to contract the normal pupils.

With regard to the threshold concentrations of eserine and pilocarpine for the normal pupil, the statements in the literature are at variance with each other. While Lewin and Guillery (1905) assume it to be 0.008% for eserine, Soki Marui (1922) did not obtain miosis with a concentration of this drug weaker than 0.02%. Likewise, Scheie and Adler were unable to obtain a miotic effect with concentrations weaker than 0.03% to 0.015%, whereas Cogan found the normal pupil still reacted to a concentration as low as 0.008%. As regards pilocarpine, Soki Marui observed very slight miosis when a concentration of 0.02% was used, whereas 0.25% was considered to be the threshold concentration by Lewin and Guillery. When comparing these different results we shall have to bear in mind what has been written above about the uncertainties inherent in this type of experiment. Besides, we must assume that the experimental conditions (number of drops instilled, illumination, etc.) have differed from one observer to the other. F. Poos (1949) has stressed the significance of the levels of illumination in investigations on the pupillary effect of greatly diluted drugs. In rabbits in which one eye had been rendered experimentally amaurotic, the effect of one drop of eserine 0.02% became apparent, while it was apparent in the normal eye only if it was light-adapted.

In all three cases, pilocarpine 0.02% had a somewhat stronger and quicker effect on the tonic pupil than on its normal fellow, especially so in the third case, where it contracted the tonic pupil from 6.5 to 4.25 mm., leaving the normal pupil unaltered.

Concentrations of eserine as low as 0.008% and even 0.004% produced under the given experimental conditions, on the whole, a measurable contraction of the normal pupil. In agreement with Soki Marui, I have repeatedly noticed a particularly lively pupillary unrest some time after the instillation. In all three cases these weak solutions of eserine had a definitely stronger miotic effect on the tonic than on the normal pupil. This also applies to prostigmine which in a 0.1% concentration in Case 2 and in a 0.04% concentration in Case 3 caused distinct narrowing of the tonic pupil, whereas it left the normal pupil unaltered.

Miosis induced by the cholinesterase-inhibiting drugs came on sometimes at about the same time in both pupils but more often sooner in the tonic than in the normal eye.

To summarize, it can be said that under the given experimental conditions, sympathicomimetics caused, on the whole, larger mydriasis in the tonic than in the nontonic eye and parasympathicomimetics caused more miosis. It must, however, be taken into consideration that, in contradistinction to the tonic pupil, which does not react to light, the size of the normal pupil will at a given moment depend not only on the effect of the drug but also on the light reflex, that is, on the intensity of illumination. Thus, the light reflex will tend to counteract an eventual slight mydriatic effect of the drug, whereas, inversely, it will reinforce a slight miotic influence. Differences in the final sizes between the two pupils are, therefore, of greater significance in tests with miotics than in those with mydriatics. Actually, they became, in the first, far more marked if the patients were at the end of the test examined in very dim light.

The increased sensitivity of the sphincter pupillae to parasympathicomimetic drugs seems to be more easily demonstrable if weak concentrations of the drugs are employed. Very probably conventional concentrations will often cause such strong reactions of both the normal and the tonic pupil as to render it difficult or even im-

possible to detect eventual differences of reaction. Thus, in Case 1, eserine 0.3% contracted both pupils to pinpoint size. As severe headaches developed afterwards, I did not repeat this test in other patients.

Response of the ciliary muscle to parasympathicomimetics.—Before discussing the influence which some of the parasympathicomimetics proved to exert on the ciliary muscle, some clinical peculiarities of the patients must be mentioned.

The first, a woman aged 40, had noticed an occasional blurring of vision of her left (affected) eye, together with a feeling of ocular discomfort. Sometimes the tonic pupil would at the same time become narrow. As a rule, it was larger than its fellow in the morning and, contracting in the course of the day, became the smaller of the two at night. Accommodation from distant to close vision required from 2 to 4 seconds and relaxation of accommodation from 5 to 8 seconds in the left eye. In the right eye accommodation was normal. Skiascopically, her refraction measured ¾ D. hyperopia in both eyes after cycloparesis by homatropine. When, however, the patient's visual acuity was determined, her subjective refraction appeared to be myopic, in the tonic eye far more so than in the nontonic eye. This functional myopia appeared, furthermore, to be extremely variable in the tonic eye, showing changes from one examination to another from ½ to 2½ D. In the course of the same examination too, the patient's subjective refraction would often show continual slight fluctuations in both the tonic and the nontonic eye. Visual acuity was 10/10 in both eyes after correction of whatever degree of apparent myopia was present at a given moment, or after correction of hyperopia if she was examined after instillation of homatropine.

In the second patient, a woman aged 40, the objective refraction was emmetropic in both eyes. Visual acuity was, as a rule, 10/10 without correction. But here too fluctuations of the subjective refraction between emmetropia and a slight degree of myopia could sometimes be observed in the right (tonic) eye, whereas the normal eye was found to be permanently emmetropic. Accommodation from a distance required 2 seconds and relaxation of accommodation 3 seconds in the tonic eye. In the normal eye it was instantaneous.

No pseudomyopia was present in the third patient, a woman aged 47. Accommodation from a distance required 3 seconds in the left (tonic) eye and relaxation of accommodation slightly more. In the right eye, accommodation was normal.

The periodical, spontaneous vacillations of the subjective refraction in the first two patients, which were no doubt due to a varying degree of mild accommodative spasm, could easily be relieved by a few drops of homatropine. It should perhaps be mentioned that this ciliary spasm was entirely different from the pseudospasm which is occasionally met with in nervous persons. In the second patient it was permanently unilateral, concerning the tonic eye only, and in the first, although bilateral, it was constantly more marked in the tonic eye. Suggestive measures did not exert the slightest influence on the symptom and, the patients' behavior was, whenever their visual acuity was tested, perfectly reasonable.

Vacillating, mild ciliary spasm does not belong to the classical symptom picture of pupillotonia. Attacks of severe spasm, however, have been occasionally mentioned in the literature. For instance, a woman patient of W. Reitsch (1925) with unilateral pupillotonia and extreme accommodative tonicity suffered from attacks of pinpoint miosis which coincided with maximal ciliary spasm and severe headaches. The affected eye was, moreover, unable to accommodate at a desired distance: once it had started, accommodation was maximal. The same phenomenon of accommodative spasm coinciding with every accommodative effort has been observed by E. Stoewer (1927) in a young woman with unilateral pupillotonia and accommodative tonicity. This phenomenon did not exist in my patients. Their mild spasm did not depend

TABLE 1.—*Influence of Highly Dilute Solutions of Eserine and Prostigmine on the Subjective Refraction in Pupillotonia* *

		Case 1, Left Eye Tonic, Objective Refraction ¾ D. Hyperopia Subjective Refraction		Case 2, Right Eye Tonic, Objective Refraction Emmetropic Subjective Refraction	
		Before Test	After 1 Hr.	Before Test	After 1 Hr.
Eserine, 0.008%	R. E.			M. ½ D.	M. 1¾ D.
	L. E.			E.	E.
Eserine, 0.004%	R. E.	E.	M. 1 D.	E. ⇄ M. ½ D.	E. ⇄ M. ½ D.
	L. E.	E. ⇄ M. 1 D.	M. 3 D.	E.	E.
Neostigmine, 0.1%	R. E.	E. ⇄ M. ½ D.	M. 2 ⇄ 3 D.	E. ⇄ M. ½ D.	M. 3½ D.
	L. E.	M. ¾ ⇄ 1¾ D.	M. 3½ ⇄ 4½ D.	E.	M. ½ D.
Neostigmine, 0.04%	R. E.	E. ⇄ M. ½ D.	M. 1½ D.	E. ⇄ M. ½ D.	M. 2½ ⇄ 3 D.
	L. E.	M. 1 ⇄ 2 D.	M. 4 D.	E.	E. ⇄ M. ½ D.
Neostigmine, 0.025%	R. E.	E. ⇄ M. ½ D.	M. 1 ⇄ 1½ D.	E. ⇄ M. ½ D.	M. 1 D.
	L. E.	M. 2 ⇄ 2½ D.	M. 4 D.	E.	E.

* One drop of the respective solutions instilled three times at five-minute intervals. Arrows indicate fluctuation of the refraction.

on the accommodative effort but was present while the patients kept their gaze fixed on a distant point. The vacillating changes of the ciliary tone which these patients presented can perhaps be paralleled with the well-known vermiform contractions of the iris sphincter and the "tonostatic" variations of the size of the tonic pupil, just as the accommodative tonicity has its counterpart in the tonicity of the pupillary reaction to near vision.

How can the slight pseudomyopia of the *nontonic* eye in the first patient be explained? According to Hayashi, Yamagiwa, Ruttner, and Kyrieleis, accommodative tonicity can be the only symptom of the pupillotonia syndrome in an otherwise normal eye. By means of pupillography, O. Lowenstein and E. D. Friedman (1942) have proved, in cases of unilateral pupillotonia, the existence of a "tonohaptic" reaction in the nontonic eye. It is, therefore, conceivable that a slight ciliary spasm may equally constitute the only symptom of pupillotonia in an eye which seems to be unaffected.

The influence of some of the parasympathicomimetic drugs on the ciliary muscle manifested itself by development of refractive myopia or by an increase of preexisting pseudomyopia. From Table 1, which shows the behavior of the subjective refraction in the first two patients under the influence of eserine and neostigmine (Prostigmin), it appears that the given concentrations of the two drugs caused an increase of refraction definitely greater in the tonic than in the nontonic eye. The hypersensitivity of the ciliary muscle of the tonic eye to these drugs was particularly evident in the second case where the nontonic eye was hardly influenced at all. In the third patient, eserine 0.008% caused but a very slight increase of the subjective refraction, equal in both eyes, whereas, here too, neostigmine 0.04% produced distinct pseudomyopia, which again was higher in the tonic eye (2¾ D., as compared with 1¼ D. in the normal eye).

As a rule, the effects of the drugs were reduced as the concentrations were reduced. Fluctuations of the refraction (indicated by ⇌ in Table 1), if present before the drugs were instilled, generally continued to be present throughout the experiments. The near point of accommodation was determined in several of these experiments. It became closer to the eye as ciliary spasm developed. The gradual development of refractive myopia was often noticed by the patients themselves who, at a given moment, would inform me that their vision was getting blurred and that they experienced a feeling of strain above their eyes. Repeatedly, headaches would ensue, which sometimes lasted until the next day. These are, of course, symptoms which are commonly met with in predisposed persons if

eserine is instilled in the normal dosage for therapeutical purposes.

Methacholine, 2.5%, produced no change of the subjective refraction.

Thus, we may conclude that the given concentrations of eserine and neostigmine exerted, in these patients, a stronger influence on the ciliary muscle of the tonic eye than of the unaffected eye, just as they had a more pronounced influence on the tonic than on the normal pupil. As compared with the sphincter pupillae, the ciliary muscle seemed to be somewhat more sensitive to neostigmine, especially if the time of onset of the effect is taken into consideration (marked by an arrow in Fig. 1). The first symptoms of developing accommodative spasm would often become apparent when the pupil had not yet reacted.

From the above, it appears that in pupillotonia increased sensitivity of the ciliary muscle—which, as we have seen, may manifest itself clinically as mild spasm—can also be demonstrated pharmacologically. The development of ciliary spasm in a tonic eye, after instillation of conventional solutions of miotics, has occasionally been mentioned in the literature (G. Voss, 1938; G. F. M. Russell, 1956). It would, however, appear that, just as in the case of the iris sphincter, weak concentrations of the parasympathicomimetics are particularly well suited to demonstrate this hypersensitivity.

These tests may also be helpful in analyzing the subjective complaints of the patients. These complaints, apart from glare due to the absence of the light reflex, are generally considered to depend on accommodative tonicity. Blurring of vision, especially if it occurs with changes of the direction of gaze, may of course be the consequence of tonic accommodation. It seems more probable, however, that the blurrings of vision in my first patient, which coincided with narrowing of the tonic pupil and ocular discomfort, were due to attacks of ciliary spasm. The following case illustrates that similar subjective symptoms may be provoked by a parasympathicomimetic drug.

A woman, aged 23, with characteristic bilateral pupillotonia and tonic accommodation was much inconvenienced by continual blurrings of vision, especially when she was reading. Besides, she stated that occasionally one of her pupils would contract to pinpoint size. This narrowing of the pupils was initiated by a feeling of ocular discomfort which she found difficult to describe. Whenever she did experience this feeling she was sure to find, on looking in a mirror, one of her pupils contracted.

Correction of the patient's manifest hyperopia of 3 D. required about 5 seconds, owing to accommodative tonicity. Shortly after she had been fully corrected, the +3 lens had to be weakened by 1 to 1½ D. owing to the development of accommodative spasm, but, after a few more seconds, she again required the original correction of +3 D. These fluctuations of her refraction subsequently repeated themselves continuously. Neostigmine 0.1% caused increase of the subjective refraction by 2½ D. As soon as her refraction started changing, that is, 20 minutes after the beginning of the experiment, the patient experienced exactly the same kind of ocular discomfort which used to accompany the sudden spontaneous contractions of her pupils. In ordinary circumstances, so she stated, she would have looked in a mirror and expected to find one of her pupils small. The discomfort caused by the patient's continual changes of refraction could be relieved by making her instil homatropine and read with suitable glasses.

Occasional sudden narrowing of the tonic pupil to pinpoint size is, of course, a well-known symptom which has been mentioned by Adie. Apparently, this sudden miosis may be accompanied by ciliary spasm, which, together with the continual changes of the ciliary tone, might be responsible for one of the patients' most troublesome subjective symptoms.

The fourth patient, a 36-year-old man with bilateral pupillotonia, complained of an occasional feeling of ocular discomfort but of no blurring of vision. Inequality

of his pupils had first been noticed about 12 years earlier. Skiascopically his refraction was 1½ D. hyperopia in both eyes. The near points of accommodation were situated, after correction of manifest hyperopia of ¾ D., at a distance of 28 cm. Visual acuity was 10/10 in both eyes. Accommodation to near vision was slightly tonic in the right eye, whereas relaxation of accommodation was instantaneous. In the left eye, accommodation was found at repeated examinations to be perfectly normal. There were no abnormal fluctuations of the subjective refraction.

The reaction of the pupils to drugs was as follows (Fig. 1). The right pupil showed a somewhat greater sensitivity to cocaine and amphetamine than the left. Methacholine 2.5% and eserine 0.008% produced a distinct and equal constriction of both pupils and pilocarpine 0.02% a slight constriction, equal in both eyes. Both pupils were insensitive to neostigmine, which, in a concentration of 0.1%, failed to contract them. None of the parasympathicomimetics caused increase of the subjective refraction in either eye.

When the patient was reexamined at long intervals, the state of his eyes was found to be unaltered. However, five years after he had first been seen he complained of occasional blurring of vision. Examination revealed the following changes in the behavior of the accommodation, as compared with five years earlier. In the right eye, accommodation from a distance had become far more tonic and relaxation, which formerly had been normal, had equally become slightly tonic. Besides, both accommodation to near vision as well as relaxation, which formerly had been normal, had now become slightly tonic in the left eye. When the patient's manifest hyperopia was corrected, some time would elapse, owing to accommodative tonicity, before his vision became clear, and very soon, apparently owing to accommodative spasm, the +lens had to be removed to make the patient see clearly. Neostigmine, 0.1%, which formerly had been ineffective, caused contraction of the right pupil from 4½ to 3¼ mm. and of the left pupil from 3½ to 2½ mm. after 70 minutes. It produced refractive myopia, fluctuating between 1 and 1½ D., in both eyes, which came on 20 minutes after the experiment had started. The drug caused but slight discomfort to the patient.

The special interest of this case lies in the fact that simultaneous development of accommodative tonicity, ciliary spasm, and increased sensitivity to neostigmine could be observed in a tonic eye in which originally none of these signs had been present.

Response of Pupil to Drugs in Syphilitic, Incomplete Absolute Pupillary Rigidity.—Only bilateral cases were available. Three cases were examined (Cases 5-7), all of whom had a history of cerebrospinal syphilis of long standing and had repeatedly undergone antisyphilitic treatment. The syphilis reactions were positive in the blood serum or the cerebrospinal fluid or in both. The pupillary reaction to light varied from very slight reaction to complete inactivity. The reaction to near vision was sluggish, with an amplitude between 1 and 2 mm., contraction lasting from 3 to 5 seconds and redilatation considerably longer. On examination with the slit lamp, the sphincter muscles showed very sluggish, spontaneous contractions. The reaction of the pupils to drugs is shown in Table 2.

Hypersensitivity of the iris sphincter to methacholine 2.5% has been taken by many observers to be pathognomonic for pupillotonia, thus allowing a differential diagnosis to be made between this condition and other pupillary disorders. Kyrieleis, however, has found miosis to occur after methacholine also in cases of complete and incomplete absolute rigidity, although less regularly and to a much less degree than in pupillotonia. From Table 2 it appears that in Cases 5 and 6 the pupils showed a distinct reaction to the drug. Although this reaction was less marked than in the majority of the above cases of pupillotonia (and others which came under my observation), a comparison between Cases 5 and 6, on one hand, and Case 4 (bilateral pupillotonia),

TABLE 2.—*Response of the Pupils to Drugs in Three Cases of Syphilitic, Bilateral, Incomplete Absolute Pupillary Rigidity*

		Case 5, Man, 58 Yr.		Case 6, Man, 68 Yr.		Case 7, Woman, 46 Yr.	
		Mm.	Min.	Mm.	Min.	Mm.	Min.
Methacholine, 2.5%	R. E.	4¼ → 3	30	4¼ → 3½	25	6¾ → 6¼	25
	L. E.	4 → 2¾		4½ → 2¾		5¾ → 4¾	
Pilocarpine, 0.02%	R. E.	4 → 2½	45	4½ → 3¾	45		
	L. E.	4 → 3¼		4¾ → 3¾			
Eserine, 0.008%	R. E.	3¾ → 1½	40	4¼ → 3	50	7½ → 5½	60
	L. E.	3¾ → 1¾		4½ → 2¾		6½ → 4¾	
Cocaine, 0.5%	R. E.	3½ → 4¾	45				
	L. E.	3½ → 4¾					
Cocaine, 0.2%	R. E.			4¼ → 6½	30		
	L. E.			4½ → 6¾			
Cocaine, 0.1%	R. E.	3¾ → 4¼	40	4½ → 5	30	no effect	
	L. E.	3¾ → 4¼		4¾ → 5			
Ephedrine, 0.5%	R. E.	4 → 5½	40	4¼ → 7	45		
	L. E.	4¼ → 5½		4½ → 7			
Amphetamine, 0.1%	R. E.	4 → 5¼	40	4¾ → 6½	25	7 → 8	60
	L. E.	3¾ → 4¼		4½ → 6½		5 → 6	
Homatropine, 0.04%	R. E.	4 → 4½	60	4¼ → 6¾	60		
	L. E.	3¾ → 4¼		4½ → 6¾			
Homatropine, 0.02%	R. E.	3¾ → 4¾	50	4½ → 5¾	55		
	L. E.	4¼ → 5		4½ → 5½			

on the other hand, shows that the differences in the amplitude of constriction were not such as to allow a differential diagnosis to be made on the basis of the methacholine test. It appeared, however, that if repeated tests were done in the same patient the response to methacholine was more constant in the tonic than in the syphilitic cases.

The effects on the pupil of very dilute solutions of both mydriatics and miotics were about the same in both conditions. These tests are, therefore, not helpful in the differential diagnosis. As the syphilitic cases were all bilateral, conclusions cannot be drawn, for reasons given above, as to possible differences between the normal and the rigid pupil as regards their reactivity to these solutions. In view of the results which were obtained with these tests in the above unilateral cases of pupillotonia, it would certainly be of interest to perform them in cases of unilateral absolute pupillary rigidity.

II. Pathogenesis of Adie's Syndrome

The sensitization of the sphincter of the pupil, in pupillotonia, to acetyl-β-methylcholine has led Scheie and Adler (1940) to believe that the underlying lesion is situated in the peripheral part of the parasympathetic pathway, that is, in the ciliary ganglion or peripheral to it. In order to explain the fact that the sphincter does not lose its reactivity to eserine, they had to assume denervation to be only partial.

This hypothesis of a peripheral site of the disturbance seems now to be fairly widely held. It seems to find support in the finding of a tonic pupillary reaction, accompanied by sensitization to methacholine, after electrocoagulation for retinal detachment (Scheie and Adler) and in experiments of R. Weekers and F. Roussel (1949), who observed characteristic tonic pupillary reactions, together with sensitization to methacholine, after retrobulbar injections of alcohol. It should, however, be noted that these workers are themselves reluctant, in view of the results of the pharmacological tests in Adie's syndrome, to draw definite conclusions from their experiments as to the pathogenesis of the latter.

Furthermore, a pathological report by F. Ruttner (1947) seems to give additional weight to this hypothesis. The only pathological changes which were encountered in his bilateral case concerned the ciliary gan-

glion, where all ganglion cells were destroyed, and the short ciliary nerves. While giving full credit to the importance of these findings, clinicians cannot help being reluctant to draw far-reaching conclusions from a single pathological investigation, considering the extremely contradictory statements which followed A. Marina's (1903) studies on the ciliary ganglion in cases of the Argyll-Robertson pupil. Ruttner felt justified to conclude from the findings in his case that, contrary to the established opinion, the parasympathetic fibers do not form synapses in the ciliary ganglion. It does not seem wise to discard, on the strength of the pathological findings in a single case, the whole of firmly established knowledge gained in the field of experimental physiology.

In 1905, H. K. Anderson proved, in experiments on cats, that after section of an oculomotor nerve within the skull, the sphincter muscle reacts to both pilocarpine and eserine, whereas, after degenerative section of the short ciliary nerves, the pupil, while reacting strongly to pilocarpine, becomes insensitive to eserine. This behavior pattern of the pre- and postganglionically denervated sphincter muscle has since been confirmed and extended by a great number of investigators. From their experiments the fact stands out that, after postganglionic interruption of the parasympathetic supply, the sphincter, while being sensitized to direct parasympathicomimetic drugs, such as acetylcholine and pilocarpine, becomes insensitive to cholinesterase-inhibiting drugs, such as eserine, DFP, etc. This is true whatever the cause of the interruption may be, e. g., excision of the ganglion or section of the short ciliary nerves (O. Foerster, O. Gagel, and W. Mahoney, 1936; S. C. Shen and W. B. Cannon, 1936; F. C. Keil and W. S. Root, 1941), retrobulbar injection of alcohol or local anesthetics (Z-M. Bacq and R. Weekers, 1949; R. Weekers and F. Roussel, 1949; C. Persichetti, 1949; H. G. Scheie and G. Ojers, 1949; P. Weinstein, 1952) or blocking of the synapses by pharmacological agents (C. Heymans and A. Hoorens, 1949; P. Weinstein, 1955).

In view of these concurring experimental findings, it would appear that the results of the pharmacological tests in my patients are not in favor of a hypothesis which claims in Adie's syndrome the existence of postganglionic parasympathetic denervation. By means of highly dilute solutions it has been shown that both the sphincter and the ciliary muscle of the tonic eye not only reacted to eserine and neostigmine but were, as a rule, distinctly more sensitive than the muscles of the normal eye. It is not compatible with the assumption of postganglionic, parasympathetic denervation, even if it is supposed to be partial, that the effector organ should become sensitized to these cholinesterase-inhibiting drugs. Analogously, the dilator muscle, although it may show after partial peripheral sympathetic denervation an atypical behavior pattern toward epinephrine and cocaine, as compared with the completely denervated muscle, does not become hypersensitive to cocaine (Foerster, Gagel, and Mahoney).

In animal experiments, Bacq and Weekers observed, after unilateral partial denervation of the sphincter by cyclodiathermy, a somewhat greater final contraction to eserine of the pupil on the operated side. The contraction came on, however, later in the operated-on eye than in its fellow. The authors explain this behavior of the partially denervated sphincter by assuming that acetylcholine, set free at the remaining intact nerve endings, by slowly diffusing into the aqueous humor comes into contact with denervated and, therefore, sensitized muscle fibers. However this may be, in my cases the tonic pupil reacted to eserine and neostigmine not only more strongly but, as a rule, also more rapidly than the normal pupil.

Gradual reappearance of the response to eserine of the cat pupil, lost after excision of the ciliary ganglion, has been observed by Anderson and, later, by E. A. Neidle (1950). It has been explained by regeneration of nerve fibers. *Hypersensitivity* of

the sphincter to the drug in pupillotonia, however, cannot be explained in this manner.

It is generally assumed that the sympathetic nerve supply reaches the globe by way not only of the long but also of the short ciliary nerves, thus passing through the ciliary ganglion. Accordingly, Foerster, Gagel, and Mahoney found the dilator muscle to be strongly sensitized to epinephrine after extirpation of the ganglion. One should therefore, if pupillotonia were the consequence of a pathological process in the ganglion, expect sensitization of the dilator to epinephrine to occur at least in some cases. Quite on the contrary, observers are unanimous in stating that the pupil is never found to react to epinephrine.

Finally, in animal experiments of Keil and Root, sensitization of the sphincter to acetylcholine developed after intracranial section of the oculomotor nerve as well as after removal of the ciliary ganglion. On the basis of these findings, these workers have questioned the validity of Scheie and Adler's hypothesis as to the pathogenesis of pupillotonia. As it is fairly certain that the syphilitic, absolutely rigid pupil is not caused by a peripheral lesion, its reaction to methacholine is of interest in this context. It is true that, in Kyrieleis' and in my own cases, it reacted to the drug less and less regularly than the tonic pupil, but these cases offer clinical evidence that in principle the pupil may show a certain degree of hypersensitivity to the drug in case of preganglionic denervation.

To summarize, we may say that the reactions of the pupil to various drugs in Adie's syndrome do not fit into the well-known patterns of either pre- or postganglionic denervation and do not warrant the assumption of a peripheral site of the causative lesion. It appears that we are as yet unable to draw conclusions from the results of the pharmacological tests as to the pathogenesis of the disease.

A second hypothesis places the disturbance not in the periphery but centrally, namely, in the region of the hypothalamic vegetative centers. It has been advocated by Kennedy, et al. (1938) on account of the great frequency with which vasomotor and other vegetative disturbances and emotional instability occur in these patients. It is furthermore based on the fact that Adie's syndrome may be associated with conditions which are supposed to be of diencephalic-hormonal origin (Stein-Leventhal's syndrome in a case of G. Hellinga and J. Groen, 1954). The concept of a disturbance situated in the hypothalamus, in a region where a center commanding the tone of the intraocular muscles is supposed to lie in close neighborhood to a central pathway of the tendon reflexes (F. Kehrer, 1937, 1938) exempts us, moreover, from the necessity of assuming the existence in Adie's syndrome of different lesions situated at far remote levels. O. Lowenstein and E. D. Friedman (1942), while acknowledging that tonic pupillary reactions may be caused by peripheral lesions, believe Adie's well-defined syndrome to be due to a heredodegenerative disorder situated in the great autonomic centers of the diencephalon and their connections with the mesencephalon.

There is ample evidence to prove the importance of a hereditary factor in the production of pupillotonia. Apart from various pupillary anomalies, such as anisocoria, hippus, etc., and accommodative tonicity, the same vasomotor disturbances which occur in the patients themselves have been met with in members of their family (M. Dressler, 1937; H. E. Meyer, 1937; G. Voss, 1938; F. Ruttner, 1947, and others). M. André-van Leeuwen (1946) has found in her patients as well as in their sibs a particularly high incidence of migraine, vasomotor disturbances, allergic and herpetic conditions, and premature canities.

In regard to the patients, described here, the following data could be elicited concerning this aspect of the problem.

CASE 1.—The patient, an emotionally unbalanced, married, childless woman, aged 40, was subject to severe attacks of migraine and was suffering from attacks of pain in her calves and feet, followed by stiffness.

She stated that eight years previously white spots had appeared on the skin of her face and throat, the latter disappearing later. About six years previously a strand of white hair had appeared together with white hairs in her right eyebrow.

Dermatological examination (Dr. L. van der Lugt) revealed a leucodermic patch on the right side of her face, that is, contralaterally to the affected eye, extending from the forehead beside the middle line to a small area on the nasal part of the upper lid and the side of the nose. Corresponding with the pigment-lacking area of the upper lid, whose lateral border gave the impression of being somewhat hyperpigmentated, there was a tuft of white hairs in the nasal part of the eyebrow. Her upper lip showed a normal hair growth, and the hairs were white on the right side of the middle line. The hair of her head, which was brown, showed a practically white lock on the right side of the middle line, and over the course of the examinations her hair turned uniformly gray. The patient was, at that time, passing through a period of severe emotional strain.

She had been subject to particularly frequent attacks of herpes simplex on the upper lip as well as on the nose and on the eyelids. Two years after she had first been seen she appeared to be suffering from herpes of the left lower lid and dendritic keratitis.

The patient had a first-born twin sister, a married childless woman. As children, the sisters had been so much alike that they had been commonly mistaken for one another, even by their mother. At the time when they came under observation the resemblance in their general appearance was less striking, probably mainly because the sister was stouter than Case 1.

Dr. P. J. Waardenburg examined the sisters with a view to decide whether they could be considered to be identical twins. Although there were some points of discrepancy—the sister, apart from being stouter than Case 1, was also 4 cm. taller—the usual measurements gave, on the whole, equal values. The shape of their nose, ears, chin, and eyebrows, the border-line of their hair, and the characteristics of their body hair were similar. In Case 1, both ear lobes were fixed, in the sister, the right ear lobe was fixed and the left mostly so. The total refraction of their eyes was equal, and there were no essential differences in the radius of the curvature and the refractive power of the cornea in the principal meridians. Their voice, facial expressions, and way of laughing were similar. Determination of the blood groups could, unfortunately, not be performed. From these findings, Dr. Waardenburg concluded that the sisters were uniovular twins.

The following points of discrepancy between the two are of special interest. In Case 1, the knee and ankle jerks were absent, whereas there were no anomalies of the nervous system in the sister. The latter had perfectly normal eyes and notably normal pupils and normal accommodation. In both sisters the greyish-blue irides had a similar pattern, but in Case 1 the left iris gave the impression of being a shade lighter than the right. In both eyes of the sister and in the right eye of Case 1, the pigment margin was well developed with some slight physiological aplasia below, whereas it was completely lacking in the left (tonic) eye of Case 1 between the 3 and 7 o'clock positions. The stroma layer margin was plainly visible in this sector. Moreover, the pupillary excrescences were, as a whole, less well developed in this eye.

There were also differences in regard to the type of their premature canities. Originally, their hair had been of the same color, but, whereas the sister's hair had turned uniformly gray at the age of 38, Case 1 had when she was first seen a white forelock. Unlike Case 1, the sister had neither vitiligo nor poliosis and had never suffered from headaches or cramps. The only fact of interest from her history was that in the course of the preceding year she had gained 10 kg. in weight and lost it again without dietary measures. The sister gave the impression of being emotionally far more

stable than Case 1. The twin sisters were only children and were unable to give information about their parents.

I have only been able to discover, in the literature, one very short report on uniovular twins (Voss), both of whom had pupillotonia. As regards vitiligo, four concordant pairs of uniovular twins have been reported and one discordant pair (P. J. Waardenburg). Twins described here were discordant for Adie's syndrome as well as for vitiligo and poliosis, and only the tonic eye of the affected twin showed atrophy of the pigment margin. I have observed similar changes in the tonic eye in other unilateral cases, and they occurred in many of those of E. Bürki (1937). This would suggest that, contrary to the opinion of Kyrieleis, changes of the pigment margin belong to the symptom picture of the pupillary disorder.

CASE 2.—The patient, a married, childless woman, aged 40, had been subject to convulsions of uncertain origin up till the age of 8 and to nocturnal enuresis until the age of 4 years. She suffered from attacks of severe migraine, and she had frequently herpes on the lips. Her hair had started to turn gray when she was about 30 years old.

The tendon reflexes of her arms and legs were low. There was a pronounced kyphoscoliosis, her neck was short, her ear lobes were fixed, her palate was ogival, and she had camptodactyly. X-ray photographs of the vertebral column showed normal vertebrae and no spina bifida.

Figure 2 shows that her maternal grandfather and three out of four maternal uncles had been prematurely gray and bald. The fourth uncle, one of her two maternal aunts, her mother, her only brother, and a cousin had been prematurely gray. Canities and calvities began in most of them at the age of about 25 years, and at the age between 30 and 35 most of the women were entirely gray and the men gray and bald. Her mother and two maternal uncles suffered from migraine.

CASE 3.—The patient, a married woman aged 47, had suffered in childhood from asthma and numb fingers. From the age of 17 years onwards she had been subject to severe attacks of migraine. Gray hairs had first appeared when she was 18 years old, and her hair was entirely white at the age of 35.

The right knee jerk and both ankle jerks were absent, and the other tendon reflexes were very feeble.

A 29-year-old nephew had noticed occasional widening of his right pupil. As a boy, he had been much inconvenienced by numb fingers, and in the cold his fingers and feet would still easily turn blue. He suffered from painful cramps in his calves and had short periods of vasomotor rhinitis. His left pupil was found to be 0.5 mm. larger than the right, but there were no other ocular anomalies. Methacholine 2.5% failed to contract his pupils.

Premature canities occurred very frequently in members of the patient's family

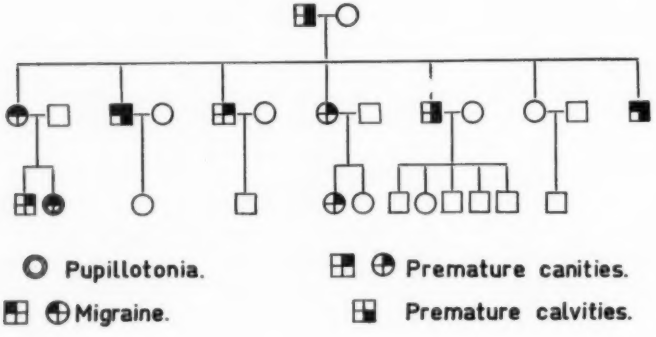

Fig. 2 (Case 2).—Pedigree.

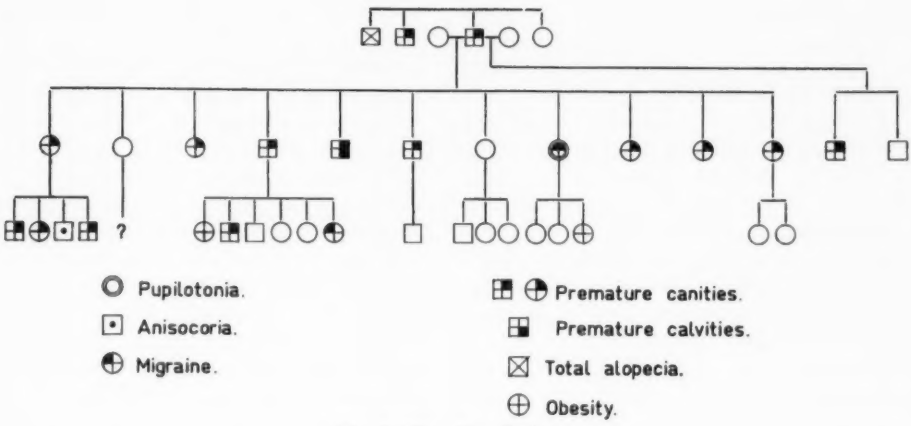

Fig. 3 (Case 3).—Pedigree.

(Fig. 3 *), appearing between the ages of 18 and 35. Some of those affected were, like the proband, entirely white at a comparatively youthful age, while in others the graying of the hair progressed but slowly. One of the proband's paternal uncles was affected by total alopecia, and a daughter and a niece were abnormally obese at a youthful age. Only one sib suffered from migraine, but other vasomotor disturbances occurred frequently. Besides, there was a particularly high incidence of asthma and other allergic conditions, such as urticaria and vasomotor rhinitis.

CASE 4.—The patient, a man aged 36, had suffered in youth from severe migraine, frostbite, numb fingers, and painful cramps in his calves. He still had at times paresthesiae in his fingers and toes. His hair turned gray at the temples at the age of 30.

In a nephew, a boy aged 7, the size of the right pupil was 5 mm. and of the left 6 mm., but there were no other ocular anomalies.

The patient's pedigree (Fig. 4) shows intrafamilial occurrence of premature cani-

* Dr. P. de Vrijer helped in collecting the data for this pedigree.

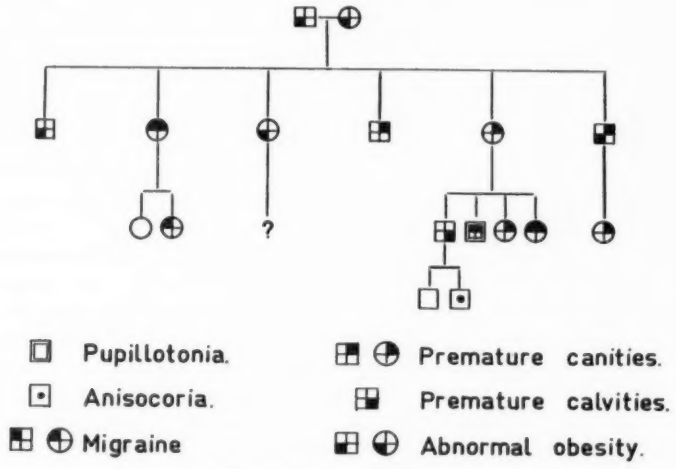

Fig. 4 (Case 4).—Pedigree.

ties and calvities, migraine, and abnormal obesity.

These cases are particularly well suited to illustrate the "morbid territory" of Adie's syndrome. Some of the anomalies occurring in the patients and their sibs have been frequently reported in conjunction with pupillotonia. Others, such as total alopecia and vitiligo and poliosis, I have been unable to discover in the literature. The question arises whether these various anomalies can, from a pathogenetic point-of-view, be brought under the same heading and whether they are able to offer an indictation as to the pathogenesis of the pupillary disorder.

An outstanding constitutional peculiarity was the frequency with which, as in André-van Leeuwen's material, premature canities and, in addition, in the pedigree of Case 2, premature calvities occurred. There is abundant clinical and experimental evidence to show that the pigmentation of the hair, skin, and iris is under the control of the autonomic nervous system. It is furthermore beyond doubt that pigmentary anomalies as well as anomalies of the hair growth may depend on disturbances of central, diencephalic, and hormonal control mechanisms. An extensive survey of arguments in favor of this assumption can be found in a paper by E. B. Hague (1944) on the Vogt-Koyanagi syndrome. Vitiligo and poliosis, which are part of the symptomatology of this syndrome, occurred in one of my patients. The importance of a constitutional basis, the "diencephalic state," for the development of, among other disturbances of the diencephalic control mechanisms ("diencephaloses"), anomalies of the hair-growth has been stressed by W. G. Sillevis Smitt (1953). Total alopecia, which occurred in the pedigree of Case 3, has been recorded by this author in patients with the diencephalic state.

Obesity in young persons, which has been recorded by C. Behr (1921) in conjunction with pupillotonia and which occurred in two of the above sibships, may suggest a diencephalic disturbance. It has been mentioned by Sillevis Smitt as one of the characteristic features of the diencephalic state.

Migraine figures in the literature in practically all large series of cases of Adie's syndrome. It occurred in all of the above patients and in the three pedigrees. In regard to migraine again, the opinion is widely held that a functional disturbance of the hypothalamus may play an important role in the production of some of the symptoms. Thus, for instance, E. C. Kunkle and H. G. Wolff (1951) consider it possible that the initial vasoconstrictive phase of the migrainous attack is caused by a discharge of autonomic hypothalamic centers. It is, therefore, noteworthy that, as I have pointed out elsewhere, sufferers from migraine (not affected by pupillotonia) and their sibs are often liable to become prematurely gray and bald, a combination which does not seem to have hitherto attracted much attention. Apart from migraine, a great variety of vasomotor disturbances occurred in my patients and their families. The high frequency of their combined occurrence with pupillotonia has figured among the arguments in favor of a hypothalamic pathogenesis of the latter. From what has been written above, it follows that the nature of the various other anomalies supports this hypothesis.

Symptoms of the dysraphic state have been reported in patients with pupillotonia. While Kyrieleis considers this combined occurrence to be perhaps more than simply coincidental, André-van Leeuwen does not feel justified in drawing conclusions from it. Only my second patient presented some clear-cut symptoms of this abnormal constitution; such minor symptoms as occurred in the others (slight prevalence of arm span over height, ogival palate, fixed ear lobes) are of too frequent occurrence in the general population to be significant. Also overlapping of the dysraphic and the diencephalic state is liable to occur in the same patient (L. Bijl, 1956).

The fact that many patients offer ample evidence of an abnormal constitution does not imply that Adie's syndrome must be

considered to be, *sensu strictiori*, a heredodegenerative disease. There is no reason to doubt that it may develop as a sequel to, for instance, an infectious disease (G. Weill and L. Reys, 1926, and others). As in persons with the diencephalic state, the central nervous system is particularly prone to harmful influences, it is conceivable that various pathogenetic factors may provoke Adie's syndrome in predisposed persons. Conclusions from a single case of twins can, of course, only be drawn with the necessary reserve. If, however, more cases of identical twins, discordant for Adie's syndrome, should come under observation, this would also support the assumption that the syndrome (and other disturbances, occurring in these families) depends on the combined influence of constitutional disposition and environmental factors.

In conclusion, it can be said that it is reasonable to assume the basis of Adie's syndrome to be an abnormal constitution, characterized by a tendency to hypothalamic reactions and disturbances, together with a diminished resistance of the hypothalamus to harmful influences. As the nature of a possible exogenous factor may in one given case remain unknown, this hypothesis renders unnecessary a rather artificial division of the syndrome into "primary" and "secondary" cases.

Summary

An investigation on the effect of very dilute solutions of drugs on the pupil and the ciliary muscle in patients with Adie's syndrome showed inter alia that the tonic pupil reacted, as a rule, to a greater extent and more rapidly to weak solutions of eserine and neostigmine (Prostigmin) than the nontonic pupil.

Some clinical peculiarities of the patients are described and attention is drawn to the following symptom, occurring in the pupillotonia syndrome: variable, mild fluctuating accommodative spasm. Greatly diluted solutions of eserine and neostigmine exerted a distinctly stronger influence on the ciliary muscle of the tonic eye, causing an increase of ciliary spasm.

The stronger and quicker reaction of the tonic pupil, as compared with the normal pupil, to indirect parasympathicomimetic drugs militates against the hypothesis which places the underlying disturbance in the ciliary ganglion or peripheral to it.

A pair of uniovular twins is described who were discordant for Adie's syndrome. The following anomalies occurred in patients and/or their sibs: premature canities and calvities, vitiligo and poliosis, total alopecia, migraine and other vasomotor disturbances, and abnormal obesity. They all point to disturbances situated in the region of the hypothalamic vegetative centers.

The evidence presented suggests that the basis of Adie's syndrome is an abnormal constitution, characterized by a tendency toward hypothalamic reactions and disturbances, together with a diminished resistance of the hypothalamus to harmful influences.

Witte de Withstraat 85.

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Pharmacological Studies of Pyrimethamine (Daraprim) in Man

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Pyrimethamine (Daraprim) has been shown to kill proliferative Toxoplasmas in vivo and in vitro.[1,2] Although it is used for the treatment of toxoplasmosis and malaria in man, few observations on its pharmacology have been made in humans maintained on the drug.

In antimicrobial therapy it is generally desirable to attain as rapidly as possible the highest concentration of a therapeutic agent consistent with acceptable levels of toxicity. The present study was undertaken (1) to determine an optimal therapeutic regimen for rapidly achieving high serum concentrations of pyrimethamine, (2) to elucidate the serum concentrations of the drug that are thereby achieved in man, and (3) to see whether a relation exists between the serum level of pyrimethamine and the bone marrow toxicity.

Methods and Materials

Nineteen patients being treated with pyrimethamine and sulfonamides were divided into three groups: 1. Multiple serum pyrimethamine assays were done on eight patients receiving 25 mg. of pyrimethamine twice daily from the onset of therapy. Since their serum concentrations of pyrimethamine reached a stable maximum slowly, other dosage schedules were investigated. 2. A group of six patients receiving 100 mg. of pyrimethamine twice the first day and 25 mg. twice a day thereafter were studied. 3. The serum pyrimethamine concentrations were determined on five additional patients who developed hematologic signs of pyrimethamine toxicity after receiving either Dosage Regimen 1 or Dosage Regimen 2.

All patients were hospitalized and received medications on the same time schedule. In all patients the times of administration of the drug and of withdrawal of samples were recorded, and in most patients studied serum was withdrawn and analyzed at several intervals during the same day. After the initial day of therapy the differences in drug concentration during any single day were negligible, and only one point is plotted for each day.

The concentration of pyrimethamine in the serum was determined with the bioassay described by Hitchings.[3] In this method a small concentration of folic acid is added to a bacterial growth medium that has been inoculated with folic acid-dependent Streptococcus faecalis. Serial dilutions of the serum to be tested are added to the inoculated medium. Since pyrimethamine and possibly active metabolic intermediates are competitive antagonists of folic acid, inhibition of the growth of the organism requiring folic acid is a function of the pyrimethamine concentration. The inhibition of bacterial growth caused by the pyrimethamine is quantitated by turbidimetric analysis of the culture.

Standardization curves and serum blanks were done with each group of sera analyzed.

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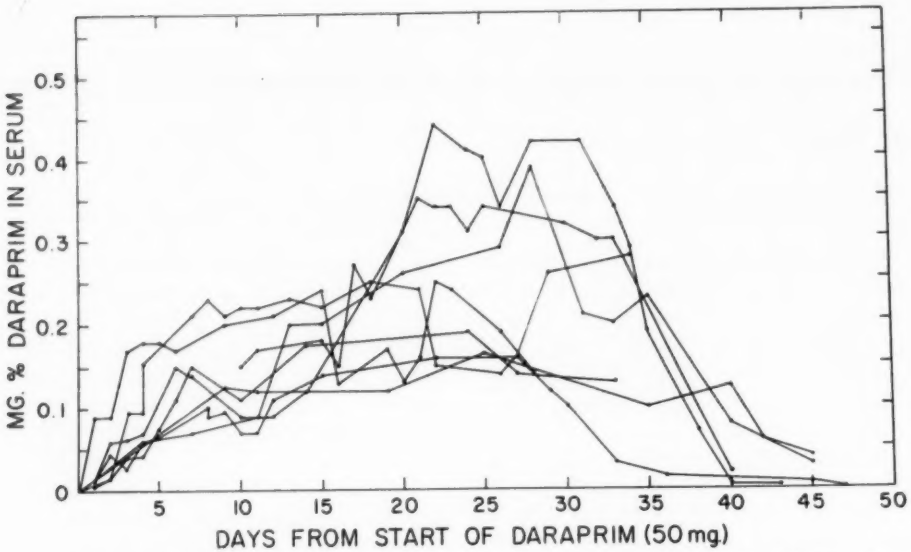

Fig. 1.—*No loading dose*: The serum pyrimethamine concentration in patients administered 25 mg. of pyrimethamine twice a day from the outset of therapy is charted. The concentrations rise slowly and vary considerably both in a given patient from day to day and between different patients on the same dosage of the drug. Pyrimethamine was discontinued between the 30th and 40th day.

Results

The results of serial serum pyrimethamine determinations on eight patients receiving 25 mg. of pyrimethamine twice a day from the onset of therapy are illustrated in Figure 1. In all, the concentrations of pyrimethamine rose gradually, but the final serum concentrations reached showed considerable variation from patient to patient. For example, during the period from 20 to 25 days, serum pyrimethamine levels varied from 0.13 mg. per 100 ml. in one patient to 0.44 mg. per 100 ml. (more than three times as much) in another (Fig. 1). There was no consistent correlation between the serum pyrimethamine level and the age or weight of the patient. In addition to variation in the pyrimethamine level from patient to patient, the serum concentrations in a single patient taking a constant dose of pyrimethamine were often different on successive days (Fig. 1). This appears similar to the fluctuations in the drug levels observed by Schmidt in monkeys given oral pyrimethamine.[4]

There are two possible explanations for these variations in pyrimethamine concentrations. Since binding sites would be saturated in patients treated for prolonged periods of time, the observed differences must be a function of either absorption or elimination. If elimination (metabolism and excretion) were sufficiently slow to cause the large differences in serum pyrimethamine concentrations, then upon cessation of therapy the disappearance of pyrimethamine from the serum of patients with high treatment serum levels should be slower than in patients with lower treatment serum pyrimethamine levels. If the rate of elimination—measured by the rate of decrease of serum levels when the same concentration has been reached—is compared in patients with different initial levels of pyrimethamine, no significant difference is observed (Fig. 2). This suggests that in all patients studied the rate of elimination was similar and that the variability in blood levels observed was due to differences in absorption of the drug. Differences in

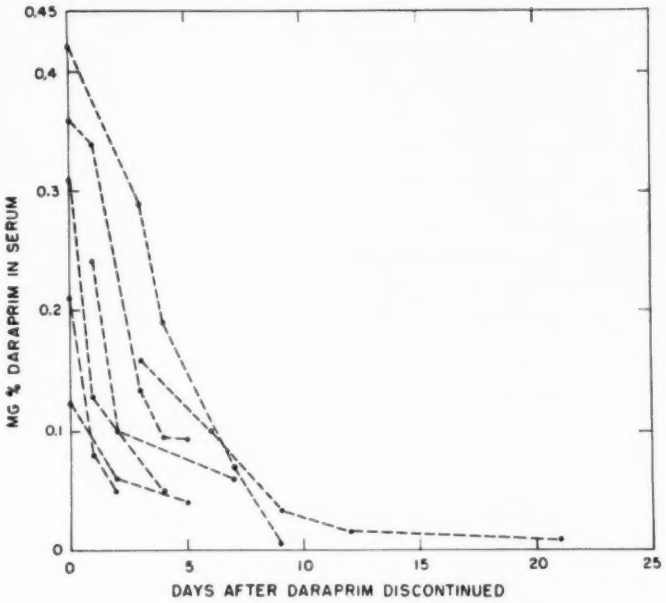

Fig. 2. — *Elimination*: The drop in serum pyrimethamine level upon the cessation of therapy is charted. The patients with higher initial levels do not eliminate pyrimethamine significantly more slowly than others.

drug absorption would also explain the fluctuations in serum pyrimethamine concentration on subsequent days in a given patient.

From the data of Figure 1 it is apparent that initially the serum pyrimethamine concentrations are low and only slowly rise to the higher levels later observed. This observation of a gradual increase in the serum concentration of the drug is consistent with the data in Figure 2 indicating that complete removal of pyrimethamine from the blood requires more than a week. This slow elimination of pyrimethamine also occurs in monkeys and in humans given a single dose of the drug.[4] On a regimen of 50 mg. a day, therefore, a subsequent dose is administered before the previous dose has been eliminated. Since the data in Figure 2 indicate that elimination varies as the serum concentration, a stable blood level can be achieved only when the serum concentration is sufficiently high to make elimination equal to intake. From these observations, it follows that a stable high blood level would be obtained by a large "loading" dose and a small "maintenance" dose.

Serum pyrimethamine levels on patients given an initial loading dose of 100 mg. of pyrimethamine twice the first day, and 25 mg. twice a day thereafter, are plotted in Figure 3. With this loading dose and subsequent maintenance dose, stable high drug levels were attained in the serum approximately two weeks earlier than when no loading dose was given (Fig. 2), though the final concentrations reached were similar with or without the loading dose. Therapy with a large initial dose and a lower maintenance dose thus appears desirable for treatment with pyrimethamine, and, though few patients have been observed, the toxicity seems no greater.

Determinations done on aqueous humor, taken after one week of therapy from five patients with serum levels at 0.1 mg. per 100 ml. or higher, revealed less than 0.005 mg. of pyrimethamine per 100 ml. in all samples despite the presence of cells and flare in the anterior chamber. Since pyrimethamine acts on the Toxoplasmas only when they are actively dividing within cells, the retinal concentration determines the efficacy of the drug, and the aqueous con-

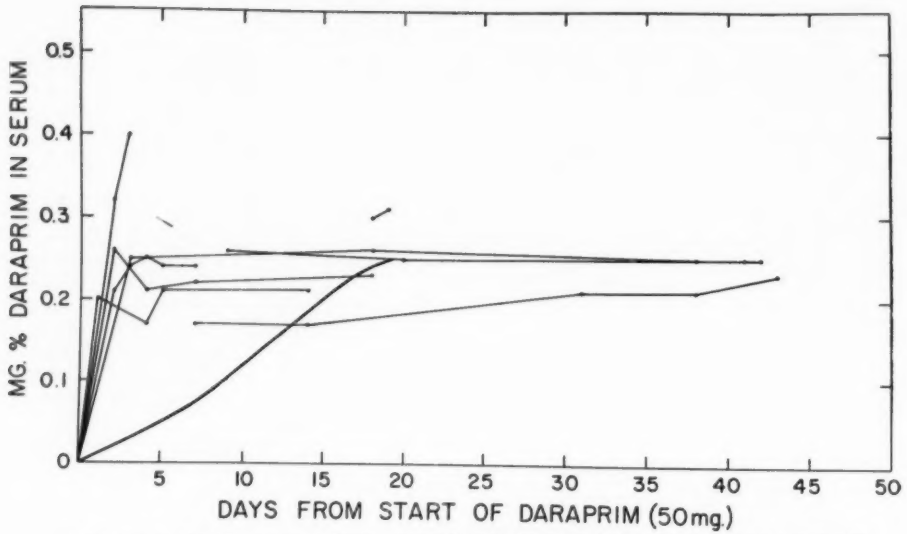

Fig. 3.—*Loading dose*: The thinner lines with visible points depict the serum pyrimethamine concentration in patients given a "loading dose" of 200 mg. of pyrimethamine the first day and 25 mg. twice a day thereafter. The heavier line is a mean curve, calculated by regression techniques, of the pyrimethamine levels of patients not given a "loading dose." The patients without a "loading dose" require about two weeks longer to reach the levels achievd by those given a "loading dose."

centration appears unrelated to the retinal concentration. Preliminary studies show a parallel in monkeys between the retinal concentration and the serum concentration (though in monkeys, as in humans, essentially no pyrimethamine is present in the aqueous). These studies also indicate that pyrimethamine is effective in ocular toxoplasmosis of other species.[8]

Though present evidence suggests that the toxicity of pyrimethamine is dose-related,[4] pyrimethamine toxicity develops only in some patients on a given therapeutic regimen. It, therefore, seemed desirable to determine whether, of patients on a given dosage schedule, those developing bone marrow depression had higher serum levels of the drug and presumably absorbed more. The data in the Table indicate that, though there was some overlapping, the patients with bone marrow depression had 1.34 times as high blood levels of pyrimethamine as the patients without signs of hematopoietic dysfunction. The probability of this difference occurring by chance is less than 0.02.

Comment

There is excellent evidence that the treatment of acute toxoplasmosis by pyrimethamine and sulfonamides in animals and in tissue culture is effective in killing the proliferative form of the organism.[3-5,7,8] In evaluating the effect of pyrimethamine on

Serum Pyrimethamine Levels in Pyrimethamine Toxicity

	Patients with Normal Hematology, Mg. %		Patients with Thrombocytopenia or Anemia, Mg. % *
1	0.16		0.44
2	0.19		0.38
3	0.26		0.25
4	0.35		0.31
5	0.23		0.31
6	0.21		0.39
7	0.25		0.16
8	0.29		0.40
9	0.26		
10	0.26		
11	0.25		
Mean	0.246	$P<0.02$	0.33

* Patients were considered to have thrombocytopenia if the platelet count was less than 100,000 per cubic millimeter or the hemoglobin was less than 9 gm.

experimental toxoplasmosis, species differences must be considered. Choi points out that the rabbit achieves only low levels of the drug when given doses of pyrimethamine similar to human doses on a per-weight basis.[6] Further experiments indicate that when larger doses are given, the drug is effective in the therapy of experimental toxoplasmosis.[7,8] Similarly, in the guinea pig greater amounts are required than would be expected when calculated on a per-weight basis from human doses in order to achieve measurable blood levels.[8] Monkeys seem to metabolize the drug slightly more rapidly than humans, but this species is most like man. In monkeys pyrimethamine is found to penetrate the blood-brain barrier and to have a slightly higher concentration in the brain than in the blood.[4] The blood-retina barrier would be expected to show similar properties to the blood-brain barrier, and preliminary experiments indicate that the pyrimethamine concentrations in the monkey retina are similar to those in blood. In humans, as well as in the animal species studied, little or no pyrimethamine is found in the aqueous. However, since the drug acts on the organism within the tissues only, the aqueous concentration appears to be of no significance.

In man, there are individual cases proven by isolation of the parasite that have responded well to pyrimethamine.[9,10] The only controlled study of the effect of pyrimethamine and sulfonamides on ocular toxoplasmosis is that of Perkins,[11] in which 101 uveitis patients were studied. In a double blind study, those patients with positive Toxoplasma dye test titers were found to respond better to the drugs than controls. The experience at the National Institutes of Health indicates that many otherwise refractory and chronic cases of uveitis respond well to pyrimethamine and sulfonamides, though this response may require two to three weeks to become manifest.[12]

Some authors have reported cases of ocular toxoplasmosis unresponsive to therapy with pyrimethamine and sulfonamides.[13] This must be evaluated with an understanding of the following statements:

1. A definite diagnosis of chronic ocular toxoplasmosis is not possible on serological grounds alone. The clinical appearance may aid in diagnosis, but without actual isolation of the parasite it is difficult to be certain of the diagnosis in a given case.

2. All reported experimental work on the therapy of toxoplasmosis has used rapidly dividing organisms. Slowly multiplying organisms are commonly isolated from man,[14] and recent work indicates that these are more resistant to the drugs. *In vitro*, the slowly multiplying 113 CE strain was killed by a concentration of pyrimethamine (Daraprim) between 1 and 5 mg. per cent in five days while the rapidly multiplying RH strain was similarly killed by a pyrimethamine concentration of 0.3 mg. per cent (The serum pyrimethamine concentrations in humans were between 0.3 and 0.4 mg. per cent). High concentrations of pyrimethamine and sulfonamide may, similarly be required in man to kill very slowly growing parasites.[15-17]

3. With foci of necrosis, as Hogan suggests, penetration of the drug to the site of infection may be impaired.

4. Either a therapeutic regimen may have been employed which does not establish sustained high concentrations of the drugs, or else a particular patient may absorb the drug very poorly.

Since some strains of Toxoplasma are relatively resistant to the drugs, and since diffusion may be impaired, there is every reason to establish as high a concentration of both pyrimethamine and the sulfonamides as possible and to maintain it for as long a time as necessary. Hematologic toxicity is related to the amount of drug absorbed. Even though toxicity is generally not severe, care in selecting the regimen as well as weekly or biweekly determinations of hematology and platelets are important. The experience of the Ophthalmology Branch of the National Institutes of Health suggests that a regimen of 100 mg. of pyrimethamine given twice the first day,

with 25 mg. of pyrimethamine given twice a day thereafter, and 1 gm. of trisulfapyrimidines given four times a day gives prompt attainment of high stable levels with an incidence of toxicity which is not alarming.

Summary

Serial serum pyrimethamine (Daraprim) determinations reveal the following: 1. Marked differences in the serum pyrimethamine concentration are seen in patients on the same therapeutic regimen. 2. The excretion of the drug when therapy is stopped, though slow, is similar for patients with different treatment blood levels. Therefore, blood level differences appear to be secondary to differences in absorption of the drug rather than differences in elimination. 3. Patients with hematologic toxicity have statistically higher serum pyrimethamine levels than nontoxic patients. 4. Unless a "loading dose" is given, the serum pyrimethamine concentration rises very slowly and two weeks or more may be required for the attainment of high stable serum drug levels.

Mr. Robert Taylor helped with the statistics and computed the regression curve of Figure 3.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health (14).

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Association of Adenovirus Type 8 with Epidemic Keratoconjunctivitis

Special Reference to the Infantile Form of the Disease

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Infection with adenovirus Type 8 appears to be regularly associated with clinical epidemic keratoconjunctivitis (EKC).[1-5] Jawetz et al.[1] isolated the prototype of this virus in 1955. Since that time, isolations of nine strains have been reported[4] to June, 1957, eight from clinical EKC and one from an unidentified conjunctivitis which may have been an infantile form of EKC. Six of the nine strains were isolated from EKC in Japan, five by us and one by Tanaka.[5]

In the present study answers were sought to the following questions: 1. What is the best technique for isolation of adenovirus Type 8? 2. How often can it be isolated from clinical EKC? 3. How long after onset can it be isolated from active cases of EKC? 4. Is "infantile EKC" also regularly associated with infection by adenovirus Type 8? (The infantile form of EKC was first described by Mitsui and Kudo[6] in 1944. It is seen in infants under two years of age and presents a different clinical picture from that of EKC in adults.) 5. How does an outbreak of pharyngoconjunctival fever (PCF) differ from an outbreak of EKC?

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Examination of Technical Problems

1. *Type of Specimen Suitable for Isolation of Adenovirus Type 8.*—From nine cases, including five cases of clinical EKC of from one to seven days' duration and four cases of conjunctivitis (three days' duration) induced by inoculation with adenovirus Type 8, virus isolation was attempted with the following materials and methods:

1. The conjunctival sac was washed with 0.5 ml. of maintenance medium * and the washing inoculated into a twice-washed HeLa-cell culture. One milliliter of the medium was added 48 hours later.

2. The conjunctival discharge was suspended in 0.5 ml. of medium and inoculated as in 1.

3. Conjunctival scrapings were suspended in 0.3 ml. of medium and inoculated into a twice-washed HeLa-cell culture. After 24 hours 0.5 ml. of medium was added, and 48 hours later an additional 1 ml. of medium was added.

During the period of observation, half of the supernate was replaced when the medium turned acid.

When conjunctival washings or suspended conjunctival discharge were used as inoculum, no cytopathogenic effect appeared in HeLa cells during a two-month observation period. When conjunctival scrapings were used as inoculum, adenovirus Type 8 was isolated from eight of the nine cases. Conjunctival scrapings were thenceforth used exclusively.

* Mixture 199, containing 10% chick serum, penicillin, and streptomycin.

2. *Tissue Culture Methods for Isolation of Adenovirus Type 8.*—In the early experiments, in which a modified Mixture 199 containing 10% chick serum and antibiotics was used, a definite cytopathogenic effect did not appear in the first culture until after 28-54 days' incubation.† The infective titer rarely exceeded 10 T. C. $D_{.50}$ per milliliter even after serial passages. With this medium, however, adenovirus Type 3 was isolated in two weeks and a high infective titer obtained. When commercially prepared Mixture 199 (supplied by Microbiological Associates, Bethesda, Md.) plus 10% chick serum and antibiotics was employed, rapid isolation of Type 8 (4-39 days, average 14 days) was obtained. The infective titer reached 40 to 320 T. C. $D_{.50}$ per milliliter after one or two subcultures. The age of the HeLa-cell cultures was important. Young cells cultivated for less than five days and overgrown cells cultivated for more than 10 days were unsatisfactory.‡ If the cells were kept in Mixture 199 with chick serum for a few days before inoculation, the appearance of cytopathogenic effects was delayed.

HeLa cells cultivated for six-eight days in tubes gave the best results. If the cytopathogenic effect did not appear within a month and the culture became acid, a blind passage after storage at or below −8 C for seven days gave a better result than further incubation of the original tube or than direct subculture without storage in the refrigerator.

3. *Stability of Adenovirus Type 8.*—In August, 1956, a conjunctival scraping mixed with 0.3 ml. of medium was sent from Kumamoto to Dr. Tanaka at the National Institute of Health, Bethesda, Md. It was sent in an ordinary glass vial by airmail without refrigeration. In spite of summer temperatures, adenovirus Type 8 remained viable and was isolated by Dr. Tanaka. Since this experience, conjunctival scrapings have often been stored at refrigerator temperature before being inoculated into HeLa cells.

Frozen at or below −8 C, adenovirus Type 8 tissue-culture material was kept for one year without demonstrable loss of titer. At room temperature it remained viable for one year with a slight loss of titer. At 37 C, a considerable loss of titer occurred in one month and the virus was not viable after three months. When lyophilized, a high titer was maintained for at least one year. When dried in the air at room temperature, no change in the titer occurred in 24 hours; after seven days of such drying, the cytopathogenic effect in HeLa cells was delayed but there was no apparent loss of titer.

Isolation of Virus and Serologic Studies on Patients

1. *Frequency of Virus Isolation.*—Up to the time of this writing, 38 strains of adenovirus Type 8 have been isolated from 49 cases of clinical EKC seen at the eye clinic (Kumamoto) between May, 1956, and June, 1958 (Table 1).§ They were isolated from 12 cases of typical EKC (adult), 12 cases of probable EKC (adult), 2 cases of unidentified EKC (adult), and 12 cases of infantile EKC.‖ Thirty-seven of the thirty-eight strains were isolated by us and one strain by Tanaka.[5] Examination of paired sera from 35 cases revealed in every instance a definite rise in neutralizing antibody to Type 8 virus during the illness.

† In some cases blind passage was required. Such cases are excluded from consideration here.

‡ Growth medium: Eagle's medium with 20% human serum, chick embryo extract, and antibiotics.

§ Until the end of 1957, virus strains and serum specimens were sent to Dr. Ernest Jawetz' laboratory, Department of Microbiology, University of California School of Medicine, San Francisco, where the typing and neutralization experiments were performed. There was a high degree of agreement between the results obtained in San Francisco and those obtained in Kumamoto. After January, 1958, the laboratory experiments on Type 8 and Type 3 were conducted in Kumamoto.

‖ Typical EKC=with subepithelial corneal opacities; probable EKC=without keratitis; unidentified EKC=patients did not return—keratitis may or may not have developed; infantile EKC=probable EKC in infants.

TABLE 1.—*Virus Isolation from Clinical EKC and PCF*

Group	Patient No.	Age, Yr.	Sex	Clinical Symptoms * Conj.	Ker.	Aden.	Syst. Sympt.	Clin. Diag.	Virus Isolations Day	APC-Type	Neutralizing Antibodies to Type 8 Acute Day	Acute Titer	Convalescent Day	Convalescent Titer
A. Adult EKC	1	27	F	F-P	—	++	—	Probable	3	8	3	<10	24	40
	2	70	F	F-P	++	+	—	Typical	3, 6	8	3	<10	80	160
	3	58	M	F	+++	±	—	Typical	3	8	3	10	36	>160
	4	13	M	F	—	+	—	Probable	1	8	1	<10	31	40
	5	19	M	F	—	+	—	Probable	3, 6, 8	8	4	<5	30	20
	6	16	F	F	++	+	—	Typical	6	8	6	<10	30	40
	7	29	M	F	—	++	—	Probable	3, 7	8	4	<10	31	40
	8	45	M	F	—	++	—	Probable	6, 8	8	9	<10	35	80
	9	40	F	F	+	—	—	Typical	2, 4, 6	8	2	<10	198	20
	10	66	F	F-C	+++	++	—	Typical	3, 5	8	3	<5	34	40
	11	23	F	F	—	—	—	Probable	2	8	2	<10	36	80
	12	32	F	F	—	—	—	Probable	3	8	3	<10	31	80
	13	32	M	F	+	—	—	Typical	3	8	3	10	44	160
	14	3	M	F	—	+	—	Probable	4	8	4	<10	34	320
	15	25	F	F	++	+	—	Typical	4	8	2	10	30	40
	16	69	M	F-C	+++	±	—	Typical	1	8	1	<10	30	80
	17	24	M	F	++	+	—	Typical	5	8	5	<10	35	80
	18	3	F	F-P	—	—	—	Probable	4	8	4	<10	39	160
	19	68	F	C-P	+	±	—	Typical	6	8	6	<10	60	160
	20	30	F	F	?	±	—	Probable	1	8	--		--	
	21	21	F	F	?	+	—	Probable	3	8	--		--	
	22	10	M	F	—	+	—	Probable	3	8	3	<10	45	160
	23	35	M	F	+++	+	—	Typical	4	8	4	<10	28	80
	24	3	F	F	—	—	—	Probable	1	8	1	<10	28	320
	25	31	F	F	+	—	—	Typical	3	8	--		--	
	26	45	F	F-P	±	±	—	Probable	3	8 †	3	<5	32	20
	27	9	M	F	—	+	—	Probable	1	3	1	<10	36	80
												<10 ‡		40 ‡
	28	14	M	F	+	++	—	Typical	4	7 †	4	<10	38	<10
												<10 §		80 §
B. Infant. EKC	1	1-1/12	M	P	—	—	+++	Infantile	7	8	7	<10	95	80
	2	6/12	F	P	—	—	++	Infantile	4	8	4	<10	38	80
	3	1-3/12	F	P	—	—	—	Infantile	6	8	6	<10	63	40
	4	5/12	M	P	—	—	+	Infantile	10	8	12	10	62	80
	5	7/12	M	F-P	—	+	—	Infantile	3	8	3	<10	31	40
	6	1-4/12	F	P	—	—	+	Infantile	5	8	10	<10	44	40
	7	4/12	M	F-P	—	—	—	Infantile	2	8	2	<10	30	320
	8	1	M	F-P	—	—	+	Infantile	3	8	3	<10	31	>320
	9	1	F	P	—	—	—	Infantile	5	8	5	<10	34	320
	10	4/12	M	P	—	—	—	Infantile	2	8	2	<10	33	160
	11	1-2/12	F	F	—	—	+	Infantile	4	8	4	<10	72	80
	12	3/12	M	P	—	—	+	Infantile	3	8	3	<10	31	320
	13	1	M	P	—	—	—	Infantile	5	2	5	<10	40	>40
												<10 ‖		>40 ¶
C. PCF	1	29	F	F	—	++	++	PCF or EKC	6, 8	1	4	10	54	<20
												<10 ¶		40 ¶
	2	4	F	F	—	++	++++	PCF	3	3	6	10	36	10
												<10 ‡		80 ‡
	3	1-6/12	F	P	—	+	+++	PCF or Inf.	3	3	3	<10	40	<20
												<10 ‡		320 ‡
	4	6/12	M	F	—	—	+++	PCF	2	3	2	<10	50	<10
												<10 ‡		20 ‡

* Conjunctivitis: F=follicular; P=pseudomembraneous; C=catarrhal. Keratitis: ?=no follow-up.
† Virus isolation and titrations by Dr. Chie Tanaka.[6]
‡ Antibodies to Type 3.
§ Antibodies to Type 7.
‖ Antibodies to Type 2.
¶ Antibodies to Type 1.

In addition to the 38 strains of adenovirus Type 8, one strain each of adenovirus Type 3, Type 7, and Type 2 was isolated.¶

¶ Type 7 strain isolated by Tanaka.[6]

Paired sera from the case yielding Type 3 virus showed a rise in antibody to both Types 3 and 8 during the illness. On an epidemiologic basis this case, in a 9-year-old

TABLE 2.—*Serial Isolation of Adenovirus Type 8 from Epidemic Keratoconjunctivitis*

	Virus Isolation on Each Day of Conjunctivitis													
Patient No. *	1	2	3	4	5	6	7	8	9	10	11	12	13	14-16
2			+			+		−				−		
5			+			+		+			−			−
6						+		−			−			
7			+				+		−					
8						+		+			−		−	−
9		+		+		+			−				−	−
10			+		+					−		−		−
(M) †				−		+		+		−		−		−

* Numbers same as in Table 1, adult EKC.
† A case of pharyngoconjunctival fever due to adenovirus Type 1.

boy, was definitely EKC. His 13-year-old brother developed an acute follicular conjunctivitis on Aug. 8, 1956. Typical subepithelial punctate keratitis was recognized on Aug. 22, and the corneal opacities were still in evidence three months later. The 9-year-old boy presented a similar conjunctivitis on Aug. 13 but did not develop keratitis. His mother suffered from a similar conjunctivitis on Aug. 16, and by Aug. 27 she had developed a keratitis that was recognized as typical of EKC and that persisted for over three months. Serological studies of the brother and mother indicated that they had been infected with adenovirus Type 8.

Paired sera from the case positive for Type 7 virus showed a definite rise in the antibody to Type 7 but not to Type 8 during the illness (Tanaka [5]).

The case which yielded Type 2 virus was probably an infantile EKC and will be described in detail below.

2. *Virus Isolation at Various Stages of Disease.*—Virus isolation was attempted on different days after the onset of conjunctivitis. The isolation of Type 8 succeeded in 38 of 48 attempts (80%) during the first five days of conjunctivitis, and in 12 of 18 attempts (67%) between the 6th and 10th day.# From the 11th day on, no isolations were achieved in any of 13 attempts. The latest isolation was obtained on the 10th day of the conjunctivitis.

Serial isolations were attempted in six cases of EKC (Table 2). Virus was readily isolated during the first week of conjunctivitis but with increasing difficulty during the second week. For comparison, serial isolations were attempted in a case of PCF due to adenovirus Type 1 (Table 2). The isolation of this virus was also easy during the first week and difficult in the second week.

3. *Virus Isolation in Infantile Form of EKC.*—Viruses were isolated from 13 of 15 cases of clinical "infantile EKC." Twelve of the thirteen strains were adenovirus Type 8, and one was adenovirus Type 2. In all cases yielding Type 8 virus there was also a definite rise in the specific neutralizing antibody to Type 8 virus during the illness.

Among 12 cases of Type 8 infection, the infantile conjunctivitis was pseudomembranous in 8 cases, follicular-pseudomembranous in 3 cases, and follicular in 1 case. Preauricular adenopathy was absent in 11 of the 12 cases, and in no instance was there any keratitis. Systemic symptoms were severe in one case, moderate in one, slight in five, and absent in five.

The case yielding Type 2 virus was a 12-month-old boy. The conjunctivitis was pseudomembranous. Keratitis, preauricular adenopathy, and systemic symptoms were absent. The amount of convalescent serum available from this patient was extremely

Statistics include isolations from experimental cases and from serial isolation experiments, but do not include trials discarded because of contamination.

TABLE 3.—*Clinical and Serological Data of PCF Cases from a Kumamoto Epidemic, 1956*

No.	Age, Yr.	Sex	Fever *	Conjunctivitis *	Corneal Opacity †	Neutral Antibody Titer		
						Time, Mo.	Type 8	Type 3
1	7	M	40.3 C (104.5 F)	Foll.	—	2	<10	80
2	10	F	"High"	Foll.	—	2	<10	80
3	7	M	39.6 C(103.3 F)	Cat.	—	2	<10	80
4	8	M	"High"	Foll.	—	2	<10	80
5	7	F	40.0 C (104 F)	Foll.	—	3	<10	160
6	13	F	39.5 C (103.1 F)	Foll.	—	2	20	80

* Fever and conjunctivitis in the acute stage; data supplied by Dr. Hiroko Okada.
† Corneal opacity at the time of bleeding, examined by slit-lamp microscopy by the present authors.

limited, and complete serological studies were not possible. However, a significant (more than fourfold) rise in antibody titer to both Type 2 and Type 8 could be demonstrated.

4. *Virus Isolation in PCF.*—In four cases of clinical PCF, virus isolation was attempted. Two of the four cases were from epidemics; the other two were sporadic and were diagnosed as "probable PCF." Adenoviruses were isolated from all of them. Three cases yielded Type 3 and the fourth case Type 1. In each instance studies of paired sera showed a rise in the specific neutralizing antibody to the homotypic virus during the illness. The conjunctivitis was pseudomembranous in one infant infected with Type 3 virus and follicular in the other three. There were definite systemic symptoms in all cases but no keratitis.

There was a moderate-sized epidemic of PCF in the suburbs of Kumamoto in July and August, 1956, associated with a swimming pool. To confirm the nature of this epidemic, late serum specimens from six children in the epidemic were examined.* They all had a high neutralizing antibody titer to adenovirus Type 3 and, except for one case, no antibody to Type 8 (Table 3).

Simultaneously with the suburban epidemic of PCF in 1956, there was a big epidemic of EKC in downtown Kumamoto. This was also transmitted in a swimming pool. About 30% of EKC cases in the present study and most of the cases reported by Tanaka,[5] came from this downtown epidemic. The differences in the clinical features of the cases seen in these two epidemics will be discussed below.

* Case 2, Group C, Table 1, came from the same epidemic.

Comment

Etiology of EKC.—Jawetz et al.[7] listed a number of criteria which must be fulfilled before a claim can be made for the identification of "the" etiologic agent of a viral disease. With respect to the role of adenovirus Type 8 in EKC, most of these criteria have been satisfied to date: (1) Specific antibodies have been demonstrated in typical cases (Jawetz et al.[8]), (2) the serologic pattern has been established as compatible with the frequency of the disease in the population (Jawetz et al.[8]), (3) volunteers have been successfully inoculated (Mitsui et al.[9]), (4) virus strains have been exchanged with and studied by other investigators (Hanna et al.[4] and Tanaka[5]), and (5) protection against the illness has been accomplished by vaccination (Mitsui et al.[10]). One criterion lacking up to the present time has been the isolation of the virus from large numbers of typical cases. This has been provided by the present study.

To date, 38 strains of adenovirus Type 8 have been isolated by us from 49 cases of clinical EKC: 12 strains from typical EKC, 12 from probable EKC, 2 from unidentified EKC, and 12 from infantile EKC. During the first five days of conjunctivitis, virus isolation was successful in 80% of the attempts. Isolation became difficult during

the second week of conjunctivitis, and we have not yet isolated the virus after the 10th day of conjunctivitis. Jawetz isolated the prototype strain of adenovirus Type 8 on the 11th day of conjunctivitis. No isolations have been reported from a later stage of the disease.

Repeated isolation of virus during the early acute stage supports the etiologic role of the isolated virus. Provided adenovirus Type 8 is not isolated from conditions other than EKC, and provided other agents are not found causing typical EKC, this disorder may be considered an etiologic entity.

From one case regarded as probable EKC on epidemiologic grounds, adenovirus Type 3 was isolated in the present study. Neutralization tests indicated that the patient suffered from a mixed infection of Type 3 and Type 8. In this case it is reasonable to assume that Type 8 virus was missed, although present. Type 3 virus was isolated quickly and gave a high infective titer, thus masking the presence of Type 8.

From another case of probable EKC (infantile), the Type 2 virus was isolated. In this case also, serologic studies indicated a mixed infection. There was a significant increase in neutralizing antibodies to both Type 2 and Type 8. The Type 2 virus could easily have masked the presence of the second virus.

Tanaka [5] has reported isolation of adenovirus Type 7 from one case of typical EKC. Serologic studies indicated an infection with this agent only. This case must be considered carefully, since subepithelial opacities, although small in number and of short duration, were unquestionably present. Tanaka [11] has further reported that five volunteers inoculated with this strain of Type 7 virus developed conjunctivitis with no keratitis. Subsequently Sugiura [12] repeated the experiment. He described a punctate keratitis in one of his three volunteers but considered it atypical. Tanaka and Sugiura agree that the illness caused by Type 7 virus may very well be a different clinical entity from that caused by Type 8.

The patient from whom Type 7 virus was isolated by Tanaka was observed clinically by one of us (Y. M.). This appeared to be a case from a big epidemic of EKC in Kumamoto transmitted in a swimming pool. Virus isolations and serologic tests definitely indicated that other cases in this epidemic were suffering from Type 8 infection. The Type 7 case could therefore only be regarded as a sporadic case of Type 7 infection. We have not yet seen an epidemic of Type 7 infection, nor has one been reported in the literature. If one should occur, however, it would seem likely that the features of the disease would resemble those of PCF or Beal's conjunctivitis (Ormsby et al.[13]) rather than those of EKC. Keratitis might appear but only exceptionally, and it would be of a "borderline" type.

Ormsby et al.[13] report that adenovirus Type 3 may also cause subepithelial punctate keratitis in adults. While this problem requires continued attention, we may say that we have not yet seen clinical EKC associated with Type 3 infection in Kumamoto. The differences in the features of epidemic Type 3 and epidemic Type 8 infections in Kumamoto are tabulated in Table 4. Type 3 has affected school children primarily. It has also involved a few adults, but keratitis typical of EKC has not so far been encountered. In our experience (1956-1958), Type 3 infection and Type 8 infec-

TABLE 4.—*Comparison of EKC and PCF Epidemics in Kumamoto, 1956-1958, According to Age of Patient (in Years)*

	Diagnosis	
	EKC	PCF *
Occurrence		
Under 2	+	+
2-14	++	+++
Over 14	+++	+
Systemic Symptoms		
Under 2	+	+++
2-14	—	+++
Over 14	—	+
Keratitis, %		
Under 2	0	0
2-14	20	0
Over 14	50	0

* Limited number of cases observed.

tion have produced different clinical entities with occasional "borderline" cases.

Differentiation of EKC and PCF.—According to our clinical observations in Japan, supported by virus isolations and antibody studies,[4] EKC and PCF can easily be differentiated from each other in epidemics. In EKC, subepithelial punctate keratitis appears in about one-half the adult cases. In PCF such a keratitis is rare and atypical. In EKC, systemic symptoms, though common in infants, are rare in adults and always milder than the systemic symptoms of PCF.

In sporadic cases the differentiation of EKC from PCF is often difficult. In adults the appearance of typical subepithelial opacities indicates the diagnosis of EKC caused by adenovirus Type 8 infection. If definite systemic symptoms are observed, PCF should be suspected. However, if both keratitis and systemic symptoms are absent, it may be impossible to differentiate the two entities by clinical examination.

Most cases of Type 3 infection in the present study had definite systemic symptoms. In the same epidemic, however, there were patients with conjunctivitis and no systemic symptoms. It has also been reported that inoculation of humans with Type 3 virus has often caused definite conjunctivitis without systemic symptoms (Bell et al.,[14] Mitsui et al.[10]). Thus the absence of systemic symptoms does not exclude PCF, nor does the absence of keratitis necessarily exclude EKC. Virus and serologic studies are required for the accurate diagnosis of such cases.

Infantile Form of EKC.—The infantile form of EKC was first described by Mitsui and Kudo[6] in 1944. They saw a considerable number of infants suffering from pseudomembranous conjunctivitis. About one-half of them had some systemic symptoms. Keratitis was absent and preauricular adenopathy exceptional. On epidemiologic grounds, however, they regarded the condition as probably related to EKC in adults. Later Mitsui[15] verified this assumption by successful cross inoculation.

In the present study it has been demonstrated that adenovirus Type 8 can be isolated from most of such infants. A definite rise in the neutralizing antibody to Type 8 virus occurs during the illness. In the majority of the cases the conjunctivitis is pseudomembranous. The pseudomembrane is often very pronounced and looks like a rubber membrane adhering to the tarsal conjunctiva; the underlying conjunctiva cannot be seen. Eversion of the lids often results in conjunctival bleeding, which may also occur spontaneously. Rarely conjunctival scarring may supervene.

Among the systemic symptoms in infants are fever, sore throat, and, less frequently, otitis media and diarrhea. They tend to be milder than the symptoms of PCF. In about one-half the cases systemic symptoms are absent, and they are severe in not more than 10%; in the first report by Mitsui and Kudo,[6] severe systemic symptoms were recorded in 6 of the 58 cases.

Adenovirus Type 3 can also cause pseudomembranous conjunctivitis in infants, as shown by Case 3, Group C, Table 1. In the absence of epidemiologic evidence, therefore, sporadic cases of infantile EKC and PCF can rarely be distinguished from each other. In epidemics, however, they can be differentiated by the frequency and severity of systemic symptoms and by the concomitance of the disease in adults.

Mode of Transmission.—EKC is known definitely to be transmissible in swimming pools. Such transmission has not been reported in the United States, but during the past two years there have been in Kumamoto two sizable epidemics of EKC known definitely to have spread in swimming pools. A swimming-pool epidemic of conjunctivitis thus does not necessarily support the identity of the disease with PCF as has been assumed in the United States.

Summary and Conclusions

Thirty-eight strains of adenovirus Type 8 have been isolated from epidemic keratoconjunctivitis in Japan. Isolation was successful in 80% of attempts during the first

five days of conjunctivitis but became increasingly difficult thereafter. Conjunctival scrapings were the best material for virus isolation, conjunctival washings or discharge proving unsatisfactory. A rise in the specific neutralizing antibody to adenovirus Type 8 was evident during the illness.

In infants less than 2 years of age, infection by adenovirus Type 8 usually manifests itself as a pseudomembranous conjunctivitis. Keratitis and preauricular adenopathy are rare, but some systemic symptoms occur in about one-half the infants. The systemic symptoms tend to be considerably milder than those of pharyngoconjunctival fever.

The relation between epidemic keratoconjunctivitis (EKC) and pharyngoconjunctival fever is discussed. Although borderline cases occur, these conditions are different clinical entities. In epidemic and in typical sporadic cases, differentiation is not difficult. In less clear-cut sporadic cases, however, virus isolation and antibody studies may be required. The results of this study support the impression that EKC is an etiologic entity caused by adenovirus Type 8. Thus laboratory evidence of adenovirus Type 8 infection can now be used to support the clinical diagnosis of EKC. Additional careful observations can be expected to aid further in establishing EKC and PCF as etiologic entities.

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Significance of Terminal Transients in Electro-Oculographic Recordings

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The Problem

An electro-oculogram (EOG) can be made to register a subject's eye movements in two dimensions if electrodes above and below the eyeball canthus control the vertical deflectors of a cathode-ray oscilloscope (CRO) and other electrodes on the sides of the eyes control the horizontal deflectors, both channels coming through suitable D. C., drift-free, amplifiers. It has been reported on fairly conclusive ground that the origin of the potentials is the positive polarity of the cornea arising from the corneoretinal potential of the eye. Since the beam of the CRO appears to move as the eye moves, a camera mounted in front of the cathode screen and left open for several seconds will register the pattern of the eye movements in a search or tracking task and the results will be similar to that of the EOG in Figure 1, which was produced in this laboratory. A description and history of work on EOG has been published by Marg.[3]

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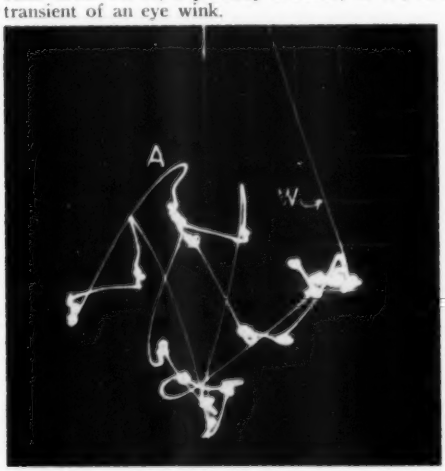
Fig. 1.—A diphasic, two-dimensional EOG from a subject who is searching for a target in a circular area. At *A*, a pathway artifact; at *W*, the transient of an eye wink.



At the same time it is also possible to send the horizontal signals to one channel of an ink-writing polygraph and the vertical signals to another channel, both to make tracings against a time base, and these may be used to measure the duration and frequency of eye fixations. The upper tracing in Figure 2 shows the vertical transients when a subject alternates his fixation from one to the other of two point-targets, requiring 30 degrees of eyeball movement up and down, with the saccadic moves occurring at about the rate of one per second. For electrodes fixed as close as possible to the eyeball canthus a movement of 30 degrees produces a signal at the site of the pick-up electrodes at about the level of 1 mv., providing balanced diphasic recording is used (involving both upper and lower electrodes).

The purpose of the present report is the exposure of a fallacious contour, mistakenly assumed to represent eyeball movement but

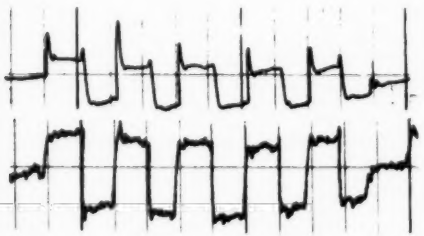


Fig. 2.—Simultaneous oscillograms from the same eye movements when the subject alternates his fixation 30 degrees between lower and upper point-targets. The upper tracing is from diphasic recording, using both upper and lower electrodes; the lower tracing shows monophasic recording from lower electrodes only.

probably due to a synchronous physiological event outside the eye. It appears that Luckiesh and Moss[2] were among the first to accomplish EOG recording with straight D. C. amplification, making oscillographic recordings on a time base line. They published samples of their tracings, and the one for vertical alternate fixation is very similar to the upper record in our Figure 2, except that their oscillogram is upside down. In our upper vertical tracing, reading from left to right, it is to be noted that at the top end of the saccadic move the potential keeps on rising for a brief moment considerably higher than that required for the upper fixation level. This effect was noted by Luckiesh and Moss, who apparently assumed that the eyeball actually overshot its target, by an inertial fling, and then returned to its normal fixation level, so they refer to it as an "overshoot" potential. In our recordings we sometimes find another brief surge at the end of the upper fixation, and this cannot be an overshoot effect because the eyeball has previously been stationary (except for tremors). The second potential surge was not present in the Luckiesh and Moss samples and is not always present in ours. On fewer occasions we also get a small apparent overshoot effect at the lower end of the downward saccadic movement. Because we believe that the potential surges at the top fixation level, especially, do not represent real eye movement and are probably adventitious potentials riding on top of the corneoretinal transients, we prefer to call them the *rider artifact*, i. e., the spurious potential seems to ride on top of the saccadic potential. We agree with Luckiesh and Moss that there is no such phenomenon for horizontal eyeball movements.

We hasten to say that no derogatory criticism attaches to the statements of Luckiesh and Moss. Indeed, they have very provocative suggestions from prevailing treatises, such as the one by Duke-Elder,[1] who gave a comprehensive review of the evidence that eye movement pathways between fixation points are seldom straight lines and frequently end in terminal hooks and loops

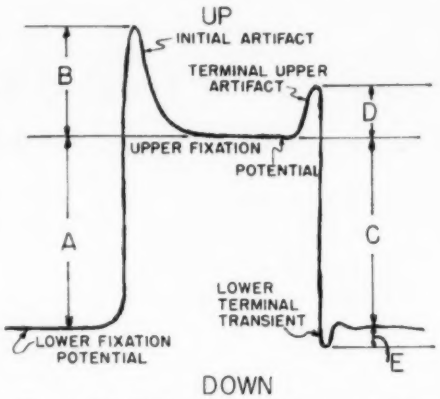


Fig. 3.—Idealized vertical EOG on a time base, drawn from a typical tracing, to show the dimensions used for measuring artifacts and transients in this report.

which are corrective adjustments to improve fixation centers. The statements of Duke-Elder are supported by the notations of Riggs et al.[4] and recently by samples of two-dimensional eye-movement plots published by Yarbus.[6] All of these were done by pure optical recordings, with no possibility of electrical artifacts. Luckiesh and Moss made interpretations on the basis of incomplete evidence, it would appear.

Methods of Measurement

The demonstration of the rider artifact requires quantification of EOG. Figure 3 was drawn to illustrate our method of measurement from an oscillographic tracing. The paper was moving to the left at a constant speed, and the recording stylus registers a height proportional to the D. C. potential coming from the eye electrodes. We may assume that the lower position of the stylus represents the potential when the eye is fixated on the lower point-target. A 30 degree change in fixation upward should stop the stylus at the upper fixation level, but the stylus keeps on going up for a short time and then comes back down to the upper fixation level. Then there is another upward potential surge just at the moment the eye starts to come down to the lower target fixation level. So, at the upper fixation level

there may be both an initial and terminal rider artifact. Figure 3 shows that the following measurements were made on each of a series of oscillographic tracings. Dimension *A* provided a measurement of the potential change for a 30 degree movement upward; *B* measured the excess potential involved in the initial rider artifact; *C* represented a measurement of the change in potential 30 degrees downward (usually the same as *A*, but occasionally different), and *D* represented the potential change of the terminal rider artifact. On rare occasions there may be a very small transient at the end of a downward saccadic move, represented by *E*. Now, $B/A \times 100$ becomes the percentage of initial rider artifact, $D/C \times 100$ becomes the percentage measurement of the terminal rider artifact, and $E/C \times 100$ is the measurement for the downward transient, which may or may not be an artifact.

Duke-Elder indicates that terminal corrective motions of the eyeball are usually less than 1 degree in amplitude, and other authors are in agreement. Recently Shackel [5] has shown that EOG potentials for movements of the eyeball less than 30 degrees are so close to being linear with angular displacement that it is scarcely worth while to use the more accurate sinusoidal progressions. Therefore terminal loops, hooks, and other fixation corrections should not exceed 3.3%, i. e., 1 degree out of the 30 in our experiments.

Size of the Rider Artifact

It happens we had 13 subjects from past research who had given us 30 degree vertical alternate fixation tracings for calibration purposes, some with only a few measures and some with more. The Table gives the results of our measurements. The initial rider artifact (*B*) was present 117 times out of 136. There were enormous individual differences, so there is no warrant for combining data. The upper terminal rider artifact (*D*) was present 50 times out of 136, with the amplitudes running much smaller, and this cannot be a corrective movement. The lower terminal rider or overshoot (*E*) was present 30 times out of 136. An examination of the Table shows that for the most part the downward terminal transient occurred in largest degree when there were heavy upward rider artifacts. The one conspicuous exception was Subject RS, whose downward terminal transients (*E*) were larger than the upward ones.

We held a provisional hypothesis that the upper rider artifacts come from some physiological structure outside of the eyeball on the upper side and that it is generated as a synchronized reflex accompanying vertical eye movement. From the ophthalmological descriptions of Duke-Elder one may assume

Percentages of Various Types of Artifacts and Transients *

		Initial Upper Artifact (B)			Terminal Upper Artifact (D)			Terminal Lower Transient (E)		
Subject	No. Measures	Av. %	Maximum %	Minimum %	Av. %	Maximum %	Minimum %	Av. %	Maximum %	Minimum %
RWJ	15	97.3	156.3	40.0	1.3	20.0	0 (14)	33.9	140.0	10.5
CEA	8	9.0	42.9	0 (3)	7.2	20.0	0 (4)	2.1	8.0	0 (5)
THB	4	83.5	94.7	58.8	0.0	0.0	0 (4)	21.1	55.0	0 (2)
TGT	7	19.7	45.8	0 (2)	7.9	23.5	0 (3)	3.0	20.8	0 (6)
KDS	3	19.9	35.0	8.0	1.3	4.0	0 (2)	0.0	0.0	0 (3)
RS	4	6.0	10.0	0 (1)	7.3	10.0	0 (1)	15.8	25.0	4.8
DHB	3	72.0	93.8	50.0	21.0	57.1	0 (1)	0.0	0.0	0 (3)
WB	5	20.5	33.3	9.1	0.0	0.0	0 (5)	0.0	0.0	0 (5)
KHJ	8	58.0	94.7	19.0	12.0	69.2	0 (4)	2.2	10.7	0 (6)
CWO	13	38.5	56.0	24.1	11.2	82.8	0 (4)	1.4	11.1	0 (11)
DGN	9	8.2	22.2	0 (3)	0.0	0.0	0 (9)	0.0	0.0	0 (9)
LH	24	18.2	72.2	0 (8)	1.8	47.1	0 (16)	0.0	0.0	0 (24)
JE	33	46.8	100.0	0 (2)	18.1	91.3	0 (19)	0.2	7.4	0 (32)

* Each artifact and terminal transient is expressed as a percentage of the EOG potential from a 30 degree vertical saccadic eye movement, the measurements made as in Figure 3. Numeral in parentheses after zeros is number of readings.

that the upper eyelid has more heavily developed muscle control than the lower eyelid, and the artifact might be a wave front from an electromyogram (EMG). This might be added to the EMG of the superior rectus with some support from the superior obliques. There is also the presence of the lacrimal gland, on the upper side, to be considered, since some small glands do give out strong electrical effects.

A Control Experiment

We devised electronic networks in such a way that one channel could carry diphasic EOG from balanced recording using both the upper and lower eye electrodes while another independent channel recorded simultaneously EOG from the lower electrode with the upper one omitted, i. e., with monophasic recording. The circuit diagram for the networks is pictured in Figure 4. If all of the EOG comes from the corneoretinal potential, then both tracings should look alike, or nearly so, and the Luckiesh-Moss assumption would be considerably justified. But if the upper transients are correctly assumed to be the rider artifact, coming from structures above the eyeball, then monophasic recording from the lower electrode alone should show either drastic reduction or complete disappearance of the transients. Referring back to Figure 2, the upper tracing was made with diphasic recording, with both upper and lower electrodes in a balanced circuit, while the lower tracing is the simultaneous record with monophasic recording from the lower electrode only, both circuits transmitting potentials from the *same eye movements.* (Monophasic recording reduced the gross amplitude of the EOG signals to ¼ or ⅕, but this was easily adjusted by raising the amplifier gain settings.)

We now secured two subjects on whom to run the new control experiment, both male students in the early part of their college careers. Subject DEB had a tendency to exhibit very large rider artifacts, and

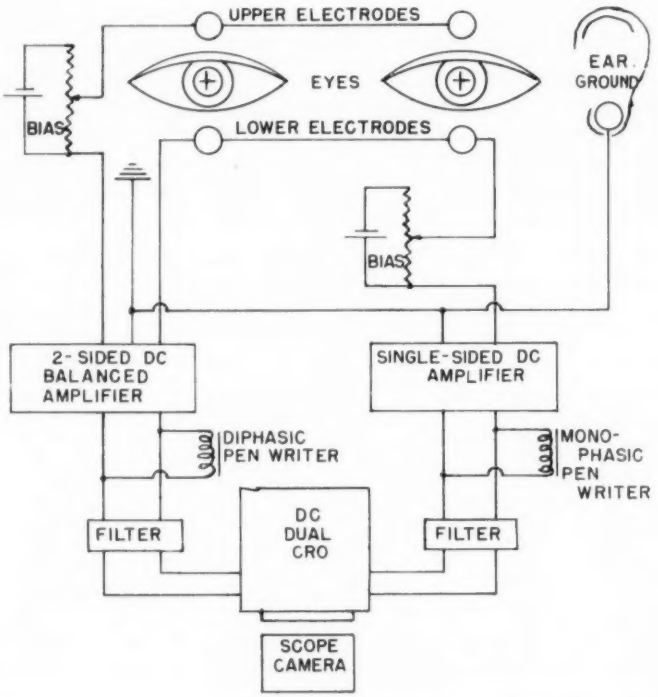


Fig. 4. — Circuit used for securing simultaneous diphasic and monophasic EOG from the same vertical eye movements.

subject PRN, on the contrary, showed rather small amounts. We shall present the findings for each separately, therefore.

Results on Subject DEB

Using diphasic recording, with both upper and lower electrodes in balanced input, the average upper initial rider artifact (*B*) for DEB was 98.5% and the probability of occurrence 48 out of 48. The maximum was 212, the minimum 50. Standard deviation was ±47.85. Using monophasic recording on these same samples, for the upper initial rider artifact, the transient was completely erased in 25 of the samples, so an average value and standard deviation would be heavily weighted by zeros. It was observed that the initial rider artifact (*B*) had a tendency to appear on monophasic recording when there were unusually large diphasic artifacts, so we have treated the 23 samples, where the artifact appeared in both channels, for a statistical comparison. In diphasic recording these 23 samples showed an average of 141%, whereas monophasic for the same samples showed an average of 25.3%. Thus, either by complete erasures or by reduction of percentages monophasic recording from the lower electrode produces heavy reductions in the artifact. Since the distributions do not overlap they are statistically reliable.

The terminal upper rider artifact (*D*) cannot be treated by averages because of the large number of zero measurements. Using diphasic recording, this transient appeared 15 times out of 48. With monophasic recording it appeared four times, another distinct reduction in probability.

The transient at the end of a 30 degree downward eye movement (*E*) could be measured only for 47 samples because of a missing tracing on one chart. It appeared nine times in diphasic recording and nine times in monophasic recording. The average for the nine measurements under diphasic recording was 4.4, whereas the average for the nine samples under monophasic recording was 11.5, with only one sample reversing the trend for higher values being on the monophasic side. The difference in means is statistically reliable at better than the 2% level, so it appears that, for this subject, on the basis of amplitude only, an hypothesis may be held that monophasic recording may increase the transient at the terminus of downward eye movements (*E*).

Results on Subject PRN

We obtained a total of 75 measurements on Subject PRN. For diphasic recording the probability was 75 out of 75 for the initial upper (*B*) rider artifact, the average was 30.9%; the maximum, 57.9%, and the minimum, 14.3%. The standard deviation was 9.03. Using monophasic recording for this same artifact, the probability of appearance was 35 out of 75. The 35 samples under diphasic recording exhibited an average of 33.6 while the monophasic was 13.8. Thus monophasic recording erased the artifact in 40 out of 75 records and reduced the amplitude markedly where complete erasure did not occur. The reduction was statistically reliable at the 1% level.

With regard to the upper terminal rider artifact (*D*), it appeared twice in the diphasic record and twice in the monophasic record but not for the same samples. The average of the diphasic record for the upper terminal rider artifact was 13.7, while the average for the monophasic was 3.9, but obviously no statistical reliability figure is possible.

The transient at the bottom of a 30 degree eyeball movement appeared 4 times in 75 for the diphasic record and did not appear at all on the monophasic record. The average of the four diphasic cases was 14.4. Contrary to the trend for DEB, monophasic recording did not increase the downward transient (*E*).

Effect on Two-Dimensional EOG

The EOG pictured in Figure 5 has plotted the Y against the X movements, so that the beam of the CRO shows the eye movements on a circular arrangement. The subject was told to fixate on the top central point and then in a clockwise direction fixate briefly on each one of eight points equally spaced so they would fall on the margin of a circle

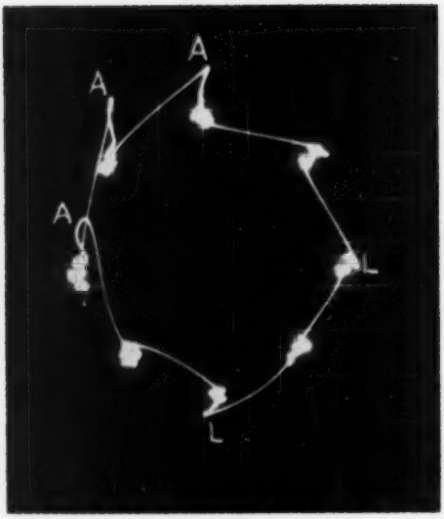


Fig. 5.—A two-dimensional EOG when the subject fixates eight points on a circle in clockwise order in 23 degree steps. Points labeled *A* show the rider artifact; points labeled *L* show small loops which may be terminal corrective transients.

of such size that the diameter would have required 30 degrees of eye movement in any direction and the distance from one point to the next was close to 23 degrees on a straight line. The resulting two-dimensional EOG photographed from the CRO shows clearly the initial upper rider artifact at the points labeled *A* where the upward vertical component in eye movement is greatest, whereas the small hooks and loops at Points *L* may be only the terminal corrections described by Duke-Elder. A terminal correction potential for eyeball fixation may either subtract or summate with the rider artifact, of course. Plots like Figure 5 were secured from 16 subjects, and all showed the typical loops of Points *A* without exception, in amounts far too large to be in agreement with the published samples of terminal corrective movements recorded by pure optical procedures.

Source of the Rider Artifact

We have already suggested that the wink musculature is one possibility for the source of the rider artifact. Figure 6 shows the vertical tracings of involuntary eye-moistening winks when the subject is not making voluntary eye movements. The sample was taken from Subject DEB with diphasic recording in the same run as for the upper tracing of Figure 2 at the same electronic amplification and the same recording paper speed. We have long ago become accustomed to the fact that it has been impossible to keep wink potentials out of EOG recording, but the wink transients are much larger for some subjects than others when recorded during eye fixations. The much weaker wink musculature of the lower eyelid may be the source for the occasional terminal transient for downward vertical eyeball movements (*E*), as shown by Subject DEB in lower-electrode monophasic recording. Wink potentials in our two-dimensional EOG's consist of large vertical loops which sometimes go completely off the scope field, looking something like the loops at *A* in Figure 5, only larger. There is one such wink transient in Figure 1. It must be remembered that our oscillographic ink tracings, plotted against time, were made with pen-writers having mechanical damping which became more and more effective at frequencies above 15 cps, thereby removing all of the spike potentials of the external eyeball muscles and allowing other EMGs to appear only at unusually heavy signal strength. This is the reason for the rather smooth envelope of the wink tracings. In two-dimensional recording from the CRO we used a low-pass filter starting at 12 cps and with about a 40 db. attenuation at 30 cps; the resulting elimination of EMG spikes is about the same as for the ink oscillograms. Without such filtering the EOG would be completely contaminated with a variety of unwanted organic potentials.

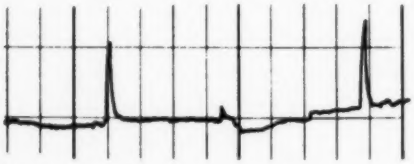


Fig. 6.—Transients from involuntary winking while fixating a target. Taken under the same conditions as in the upper tracing of Figure 2.

On the assumption that the neuromuscular control from the central nervous system is such that reduced wink reflexes are synchronous with vertical eye movements, we decided to see if people with large wink potentials were prone to have large rider artifacts. (It is a fact that this association can be crudely tested merely by resting one's finger on the upper eyelid, lightly, to feel the movement of the lid when vertical eye movements are made.) Figure 7 shows a plot from 16 subjects, which include those of the Table, in which the average involuntary wink potential-amplitude of each, taken during five minutes of fixation time (cumulative from fixations between movement exercises) is plotted against the percentage value of the rider artifact. The two subjects with the smallest wink potentials had the smallest artifact, and the one subject with the greatest wink potential had the largest artifact, but the others showed such a wide scatter that a product-moment correlation gives a value of $r=0.41$. An attempt to study wink frequency in a similar fashion yielded nothing.

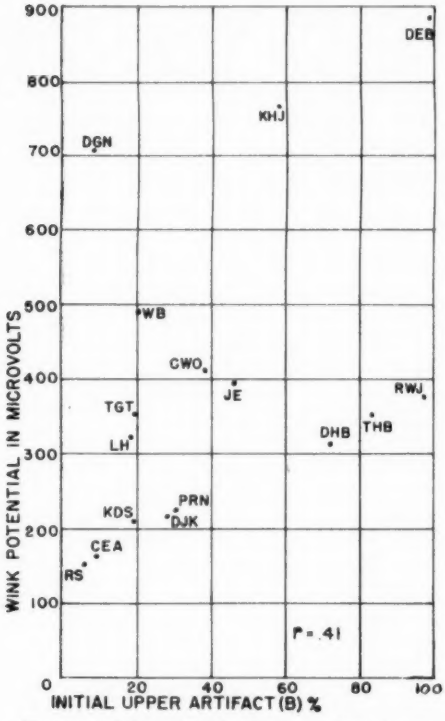


Fig. 7.—Wink amplitude plotted against the percentage of the rider artifact. Initials indicate which of these subjects are the same as in the Table. The product-moment correlation is 0.41.

There seems to be no evidence available on the possible influence of other physiological structures around the eyeball, such as the glands. Until more penetrating anatomical-functional analysis can be made, we cannot be completely certain of the origin of the rider artifact. That it is an artifact, with respect to the two-dimensional plotting of eye movement pathways, seems to us to be the best interpretation from the data offered.

Summary and Conclusions

With the availability of good electronic equipment for making two-dimensional electro-oculogram (EOG) plots it becomes certain that this technology will come into use more and more for researches on visual skills and for the diagnosis of eye movement defects. A final accounting seems desirable to avoid fruitless expenditure of time when the errors in EOG are not realized.

The precise plotting of eye-movement pathways by EOG is doubtful at the present time. Only with subjects highly selected for small rider artifacts and with the use of monophasic recording from lower eye electrodes can we reduce physiological-electrical distortion down to usable levels.

With care, EOG can be used for plotting two-dimensional expositions of the fixations of the eye, since between initial and terminal rider artifacts there is usually a fairly correct rendition of the fixation potential. Because visual information is gathered largely during the time of eye fixations, this fact is fortunate for the analysis of many visual skills.

Time measurements between fixations and the frequency of fixations per unit of time are well exhibited in recording vertical and

horizontal saccadic transients separately on time-base oscillograms.

Code 2132, Building 4, U. S. N. Electronics Laboratory (52).

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Surgical Treatment of Scleromalacia Perforans

MALCOLM W. BICK, M.D., Springfield, Mass.

Scleromalacia perforans is an extremely rare disease. It's present designation was given in 1934, by van der Hoeve.[1] From its first description in 1893, by Holthouse, until 1951, only 19 cases had been reported.[2] Since then a cursory review of the literature reveals an additional 8 cases, making a total of 27. Walter Bauer and his associates at the arthritis clinic of the Massachusetts General Hospital, in their series of 296 patients with rheumatoid arthritis, found no case of scleromalacia perforans.[3] Of 465 cases of rheumatoid arthritis studied at The Johns Hopkins Hospital by Smith, only 1 patient suffered from scleromalacia perforans.[4] Microscopic evidence of scleromalacia is apparently more frequent. In a survey in 1943 by Fingerman and Andrus, 66 autopsies were reported on patients suffering from rheumatoid arthritis and scleromalacia was found microscopically in 3 cases.[5]

Clinical Course

In 1951, Sorsby described the scleromalacia perforans syndrome as follows[6]:

> Though generally chronic and slowly progressive, scleromalacia may set in abruptly and run a rapid course, leading to blindness within a few weeks.
>
> The earliest changes suggest a patch of localized scleritis. The affected surface rapidly assumes a sloughy appearance which in turn gives way to an obvious defect in the sclera through which the bluish choroid can be seen. These defects are generally multiple and may occur anywhere on the sclera. . . . The cornea may become involved almost exclusively. A sloughing peripheral ulcer spreads steadily toward the center; there is a loss of substance and ultimately, perforation. If the intercalary part of the sclera is involved, aqueous may escape or the iris may protrude.
>
> Arthritis of the rheumatoid type is almost always present. . . . All measures have proved ineffective in the treatment of this condition.

Pathology

The first complete pathological description of this disease was in 1938, by Verhoeff and King.[7] Their case was a man suffering from rheumatoid arthritis whose eye was removed because of extensive scleromalacia, reduced vision, and severe pain. Sections showed extensive attenuation of the sclera which appeared to start as a degeneration of the collagen fibrils. Surrounding this degenerating scleral material, pallisading fibroblasts, and chronic inflammatory cells appeared (Fig. 1). These authors describe the degenerating scleral material as a sequestrum and the pathological process essentially as that of scleral abscess formation. From their description of the sections it was apparent that these observers appreciated the fact that new fibroblastic proliferation was an essential feature of the pathologic process, and, indeed, a certain amount of spontaneous fibroblastic repair accompanied degeneration in adjacent areas.

This reparative feature of the disease was also elaborated by Hobbs, who attempted to evaluate the effect of cortisone both locally and systemically on the pathology.[8] He described the eye of a patient with rheumatoid disease associated with scleromalacia who had received a course of systemic cortisone a short time before he died of pericarditis. He observed that a new perforation had occurred while the patient was on a systemic dose of 100 mg. a day. Hobbs felt that intensive local cor-

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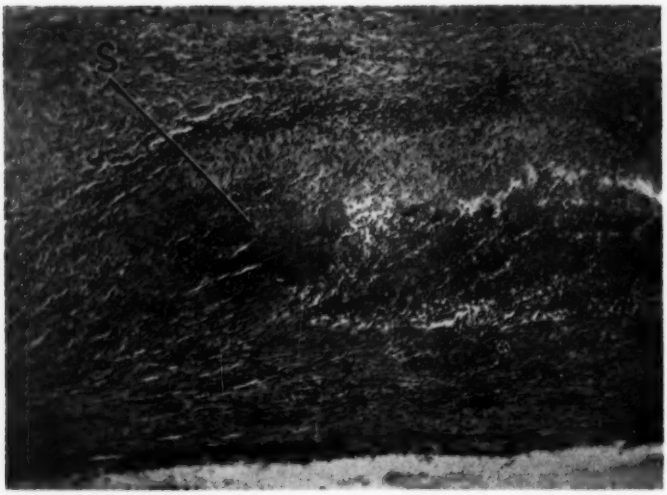

Fig. 1. — Pathological section from Verhoeff's original description of pathological process, showing necrotic nodule of sclera. Reproduced with permission from Verhoeff, F. H., and King, M. J.: *Arch. Ophth.* 20:1013-1035, 1938.

tisone was helpful during the weeks prior to the patient's death, in that he developed no new nodules during this period. The pathology in this case was no different in any respect from that described by Verhoeff and King in 1938, in a patient who had received no steroid therapy. However, an important observation made by Hobbs was the suggestion that scleromalacia was a manifestation of collagen disease and that his patient had other manifestations of a wide-spread connective-tissue disorder.

In a discussion of Hobb's paper, Duke-Elder pleaded for simplicity in describing this condition and suggested that it be called rheumatoid nodule of the sclera. After reading the attempts of some authors to classify various types of scleromalacia perforans into unintelligible subdivisions, I am in sympathy with this approach. However, it would be an oversimplification to state that this disease is simply an ocular manifestation of rheumatoid arthritis.

Harbert and McPherson described an interesting case of a 31-year-old man who developed scleral nodules with necrosis as a manifestation of periarteritis nodosa.[9] François reported a 71-year-old woman with scleromalacia perforans associated with pemphigus and severe arthritis in which the eye had to be removed.[2] The role of endocrine dysfunction has recently been propounded by Roset and his associates as a cause of scleromalacia.[10] A 78-year-old woman, acromegalic since the age of 35, developed panophthalmitis secondary to scleromalacia perforans. They reported a second case in a 38-year-old woman with ovarian dysfunction. These authors did not seem to be impressed by the fact that each of these women suffered from rheumatoid arthritis as well.

A very dramatic description of the pathological findings is contained in a report by Kiehle, who examined the eyes of a bed-ridden arthritic who died.[11] Both corneas were opaque. The sclera was completely absent to the equator, where the eyes were fixed to the adnexa. The tarsus was attached directly to the globe. Behind the equator the sclera appeared to be normal.

Therapy

The therapeutic approach to this disease may be divided into medical and surgical, and the literature is not voluminous.

In 1937, Oast described a case in which local ultraviolet light was thought to be beneficial.[12] Hobbs reported the beneficial effect of local cortisone, while systemic treatment appeared to be valueless.[8]

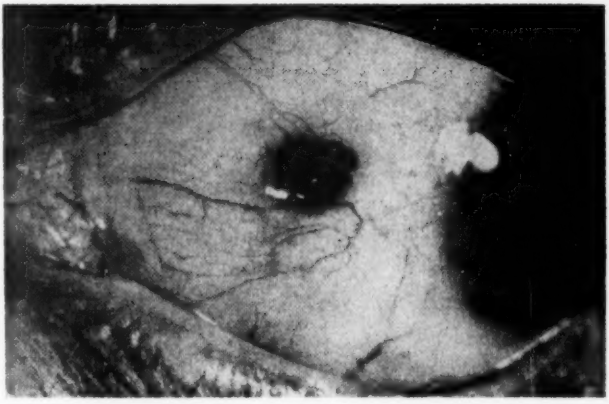

Fig. 2. — Preoperative appearance in Paufique's case of a small discrete nodule of scleromalacia. Reproduced with permission from Paufique, L., and Moreau, P. G.: *Ann. ocul.* 186:1065-1076, 1953; Paris, Gaston Doin & Cie.

Aside from the enucleation of many eyes that has been performed as the treatment of choice, efforts have been made to maintain the integrity of the eye by reinforcing it.

Van der Hoeve described the use of a conjunctival flap and a buccal mucosa graft, but all vision was lost.[1] In 1934, Eber reported a successful flap operation in a small localized perforation with a prolapsed iris.[13] Renard, in 1953, reported failure of a buccal mucous membrane graft as well as a donor scleral graft but in another case had successfully employed autogenous auricular cartilage to replace a small scleral defect.[14] In the same year, Paufique described a trephine operation in a small isolated scleral perforation.[15] He obtained a good result with a donor scleral button (Figs. 2 and 3).

In 1956, the work of Armstrong and McGovern reported in the Australian literature was unknown to me. My solution to the problem was similar to theirs, although the details of the surgical technique were not identical. The results in both their case and mine were encouraging.[16]

Report of Case

A 60-year-old man was seen at his home at the request of his family physician on July 31, 1956, because of progressive enlargement of a lesion of the left eye which had been followed over a three-month period. The family physician had described the onset of the lesion as a red, vascular area which had slowly grown in size and changed in color. A previous consultant had recommended the use of local neomycin

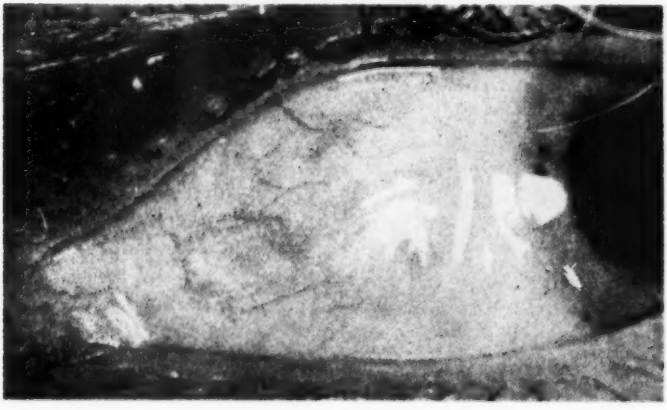

Fig. 3. — Postoperative appearance after scleral transplant in Paufique's case. Reproduced with permission from Paufique, L., and Moreau, P. G.: *Ann. ocul.* 186: 1065-1076, 1953; Paris, Gaston Doin & Cie.

and hydrocortisone and warned the patient that the loss of the eye was imminent. The only significant medical event prior to the development of rheumatoid arthritis was an appendectomy in 1920. His arthritis started in 1943, and from that time on it was a progressive story of increasing stiffness of the joints of the feet, legs, shoulders, hands, elbows, and wrists and, finally, involvement of the spine. In 1945, a diagnosis of a gastric ulcer was made, and this was controlled by diet and alkalies. In 1951, the arthritis of the legs had become so severe that the patient had to give up his occupation as a stationary engineer and turn to weaving as a trade. In 1952, a polyp of the sigmoid colon was excised and found to contain a Grade 1 carcinoma in situ. In 1955, an arthroplasty of the left hip with an Eicher head prosthesis was carried out for intractable pain. In October, 1955, the patient was admitted to the hospital with a diagnosis of pneumonitis of four days' duration. The patient remained in the hospital for a period of three and one-half months with a bizarre pneumonitis which failed to respond to any of the antibiotics. It finally resolved spontaneously. During this period of hospitalization the patient developed decubitus ulcers over the sacrum, over the back of the legs, and on the heel of the foot. He was treated with general supportive measures, including several blood transfusions. However, despite the fact that the lung condition improved, the decubitus sores over the back and on the legs were in bad condition when the patient requested discharge from the hospital against advice. During this hospitalization the suggestion was made that the patient might be suffering from some general collagen disorder in addition to his rheumatoid arthritis. Following this extensive hospitalization, the patient was nursed at home with the help of his wife and the Visiting Nurse Association. After a period of two to three months, the decubitus ulcers healed. He was able to sit up in a chair and get about with difficulty with the assistance of crutches. Three months prior to my visit the patient complained of irritation of the left eye and gradually developed blurred vision. Examination was carried out in the home of the patient, with the patient seated in a chair. Vision in the right eye was 20/20 corrected; vision in the left eye, 10/200. Externally, the lids, lacrimal apparatus, extraocular motility, and pupillary reactions were normal. External appearance of the right eye was essentially normal throughout except for some duskiness in the region of the ciliary body which could be made out through what appeared to be a slightly attenuated sclera. In the left eye, extending from the 9 o'clock position downward to the 6 o'clock position in the paralimbal region and extending backward toward the equator for a distance of approximately 1 cm., was a large darkly colored bulging mass lying underneath the conjunctiva (Fig. 4A). The conjunctiva appeared to be intact over this extruding uveal tissue, and there was considerable dilatation of blood vessels over the area. In the adjacent cornea, extending from approximately 10 to 6 o'clock was a marginal sulcus extending into the cornea for approximately one-half of its depth. Through a hand-slit lamp the patient had a 1+ aqueous flare, although no K. P. deposits could be made out. The cornea itself, in the region of the sulcus, appeared to be somewhat edematous. Fundus details were made out hazily, but no gross fundus lesion was observed. In the right eye funduscopic findings were essentially normal except for a Grade I arteriosclerosis. A diagnosis of scleromalacia perforans associated with rheumatoid polyarthritis was made, and it was decided to admit the patient to the hospital in an effort to prevent the loss of the eye. The patient entered the hospital on Aug. 8, 1956. Physical examination in the hospital showed a very crippled white man lying in bed with the eye in the condition previously described. Physical findings were primarily related to his arthritis; he was unable to open his mouth more than 35% because of arthritis of the temporomandibular joints. His neck was very rigid due to the arthritis. Motion of all of the joints was painful and limited.

Figure 4A

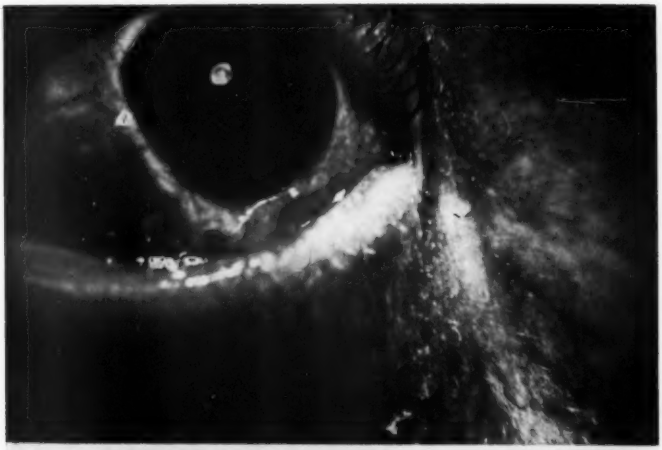

Figure 4B

Figure 4C

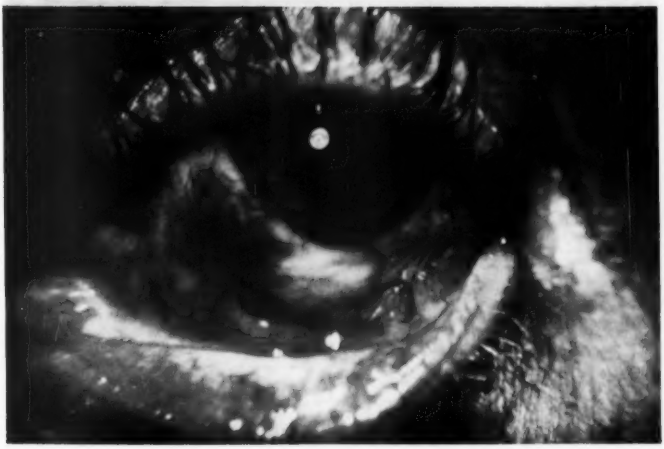

Fig. 4A.—Preoperative condition of eye showing involvement of entire lower nasal quadrant of globe with adjacent corneal necrosis.

Fig. 4B.—Six weeks after transplant the fascia lata is seen covering the defect.

Fig. 4C.—Six months after grafting the fascia lata appears attenuated over the area of the original disease. There was no recurrence of uveal prolapse or further change in the appearance of the eye.

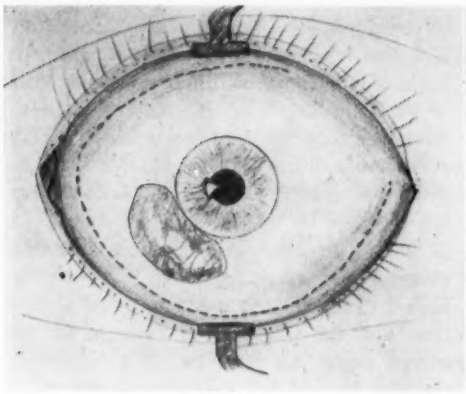

Figure 5A

Fig. 5A.—The conjunctiva was incised almost back to the fornix and reflected forward.

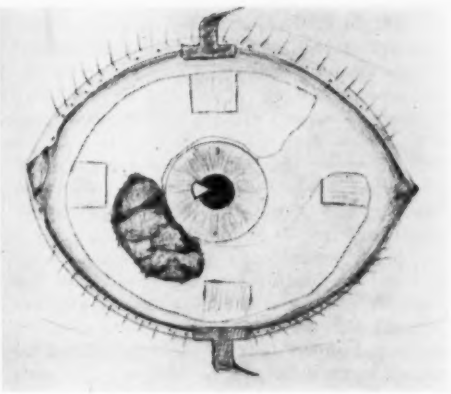

Figure 5B

Fig. 5B.—The area from which the conjunctiva and Tenon's capsule have been dissected is shown as denuded. The lesion is exposed, and the recti muscle insertions are now available for attachment of the graft.

There was considerable wasting of the muscles of the thigh and of the lower leg. Over the back were the scars from several healed decubitus sores. The cardiovascular system was essentially normal. Electrocardiographic studies indicated no abnormality. Laboratory studies showed a hemoglobin of 12.3 gm. %, a 42% hematocrit, 8,150 white cells with a differential count of 67% neutrophils, of 28% lymphocytes, and of 5% eosinophils. Corrected sedimentation rate was 37 mm. per hour. Urinalysis showed no abnormality. On the second hospital day the operations described in the operative notes were performed. The note of Arthur Mittnacht, M.D., follows.

The right thigh was prepared with PhisoHex and aqueous Zephiran (1:1,000) and draped in the usual fashion. A 4 inch longitudinal incision was made over the lateral aspect of the distal third of the thigh; dissection was carried down to the fascia lata. A section of this was resected measuring 4 inches in length and 2 inches in diameter. A small muscle biopsy was then taken from the vastus lateralis. The wound was then closed using #000 interrupted silk sutures in the skin. The patient was then turned over to Dr. Bick who then transplanted the fascia to the orbit.

Description of operation by me (Figs. 5A-D).

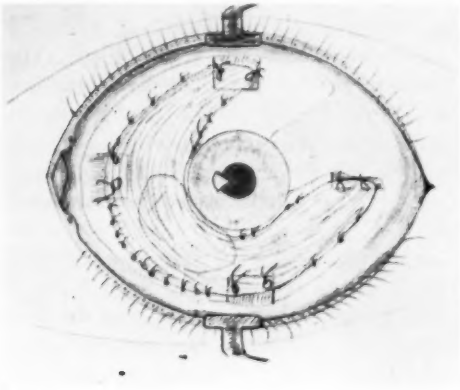

Fig. 5C.—The fascia lata has been attached to the insertions of the recti muscles with 0000 mild chromic absorbable surgical (gut) sutures and to sound sclera with 000000 mild chromic absorbable surgical sutures.

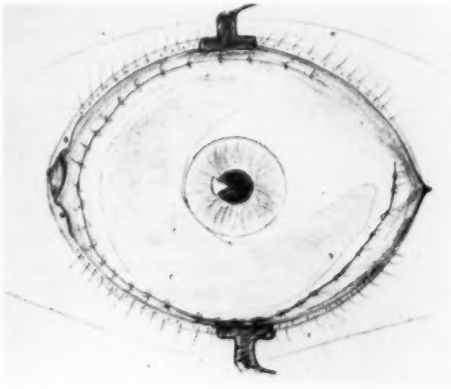

Fig. 5D.—The graft is seen lying beneath conjunctiva and Tenon's capsule. The conjunctival wound has been closed with interrupted 000000 mild chromic absorbable surgical (gut) sutures.

Under general anesthesia the patient was prepared and draped in the usual fashion and the left eye was studied. It was found that the entire lower nasal quadrant of the sclera was involved by a thinning process, and that the uveal tissue lay just under the conjunctiva. In addition, there was a small sulcus near the limbus deepest at the seven o'clock position but extending from ten to six o'clock. Several blood vessels invaded this sulcus. Extending from the limbal area backward for a distance of approximately one centimeter and upward and downward for a distance of about one centimeter, there was a black grape-like mass extending under the conjunctiva. The conjunctiva was incised almost back at the fornix from the external rectus muscle to the inferior rectus muscle, then over the internus and finally, up to the superior rectus. The flap of conjunctiva was dissected forward and great care was exerted not to perforate the globe over the region of the extremely thin sclera. It was possible to turn down an intact flap of conjunctiva. At this point, the hand cautery was used to coagulate several dilated blood vessels and several oozing episcleral vessels. Also, a direct cauterization over the thin sclera was accomplished by using the ball of the Todd hand cautery. This produced immediate flattening of the prolapsed uveal tissue. The piece of fascia lata which had been prepared in advance was then trimmed down to envelop the eye very much in the fashion of a second layer of sclera. It was cut out to conform to the limbal curve for the entire circumference of the eye. The fascia lata was sutured securely to the four recti muscles by means of #0000 double armed chromic catgut, two sutures to each rectus muscle. The suturing was accomplished in such a manner as to make considerable tension over the perforated area. The free edge of fascia lata was fixed to the sclera by means of interrupted #000000 mild chromic catgut. These sutures were found to be important to prevent the fascia lata from sliding forward, since the greatest tension was along the anterior edge of the graft. The reflected conjunctival flap was then closed by means of #000000 interrupted mild chromic catgut. The eye was dressed with terramycin ophthalmic ointment and a pressure dressing applied. The patient was returned to the ward in good condition.

The patient withstood the procedures well; the eye was dressed on the third postoperative day, and the graft was found to be firmly in place. There was considerable edema of the conjunctiva, and on the fifth postoperative day it was noted for the first time that there was some sloughing of the conjunctiva in the 7 o'clock position. The eye was dressed every second day with oxytetracycline (Terramycin) ophthalmic ointment. On the 17th postoperative day it appeared that the conjunctiva would close in spontaneously and it was felt safe to discharge the patient from the hospital. After the patient's discharge from the hospital, the eye was dressed at home every second day by the visiting nurse for a period of three weeks. Six weeks after the surgery the conjunctiva had completely healed (Fig. 4B). It was also noted at this time that the sulcus at the margin of the cornea extending from the 10 to 6 o'clock position had all but disappeared and what appeared to be normal corneal tissue had replaced this defect. The patient stated that his vision was beginning to improve. As soon as the conjunctiva had healed, the papient was placed on local neomycin and hydrocortisone ophthalmic solution, 0.5% every two hours while awake. The eye was dressed with a similar ointment at night. This treatment was continued for one month. At this time the inflammatory reaction appeared to be almost completely at an end, and all therapy was stopped. Refraction six months postoperatively brought the vision up to $20/20-2$ with the following correction: O. S. $+75-3.00\times60$. It was noted at this time that several changes had occurred in the eye (Fig. 4C). It was found that the pupil of the left eye no longer reacted to light or in accommodation and that a marked degree of heterochromia had developed. The graft which could be seen very prominently under the conjunctiva had now become less prominent and seemed to be merging with the scleral tissue. The sulcus which had previously been identified along the corneal margin was no longer visible; the anterior chamber was of normal depth; the fundus showed no abnormalities, and details could be made out without difficulty. The aqueous flare was no longer present. A somewhat disturbing sign was a small area of discoloration in the 7 o'clock position corresponding to the area where the conjunctiva had sloughed postoperatively. However, this area, which had

not increased in size for over a year, was thought to be due to the migration of pigment through a somewhat attenuated fascia lata in this location. In 14 months there had been no evidence of any recurrence or any inflammatory reaction in the eye. In August, 1957, one year after the operation, the patient complained of some blurring of vision. Refraction was carried out as follows: O. S. $-3.25\times75=20/20+2$.

In November, 1957, the patient died very suddenly from a massive aspiration of stomach contents during an x-ray examination. Unfortunately, the pathologist failed to secure the eyes at the postmortem examination. We are therefore dependent on the clinical observations to know the fate of the graft. However, the valuable contribution of Armstrong and McGovern, summarized in the discussion, indicates that the graft survives and vascularization from adjacent sclera and conjunctiva occurs.[16]

Comment

The scleromalacia process was controlled by the reinforcement of the globe with a fascia lata graft for a period of 15 months until the patient died.

When the case was presented to the New England Ophthalmological Society, Dr. Frederick Verhoeff wondered why it was necessary to apply such a large graft to cover a relatively smaller area. It was my feeling that a large bed of uninvolved tissue might ensure a more successful "take" and, in addition, would provide attachment for the graft in healthier tissue. The insertions of the extraocular muscles provided convenient anchorage for the graft.

Dr. Trygve Gunderson wondered why a scleral graft could not be employed. It was my opinion that in a large irregular defect a scleral transplant would be technically more difficult. In a small discrete defect, a scleral graft would be the treatment of choice, but in a rapidly advancing scleromalacia it would be difficult to know how extensive to make the graft.

Special mention must be made of the work of Armstrong and McGovern, of Australia, who are the only others, to my knowledge, to use a fascia lata transplant. Their paper had not been catalogued at the time that this problem confronted me. If I had known of their work, I might have proceeded with greater certainty. In their case, three operations were performed, and in the course of the fourth, the patient died of cardiac arrest. This unfortunate outcome provided a pathological study of the graft. It was clear from their sections that the graft became vascularized and incorporated as a supplementary layer of tissue (Fig. 6). Dr. Armstrong wrote me that he felt that use

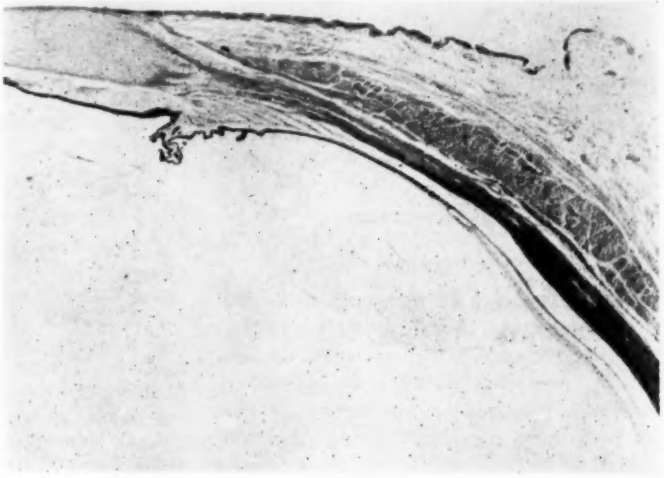

Fig. 6.—Necrotic sclera with overlying fascia lata graft in situ several months after transplant. The graft is vascularized by adjacent vessels. Reproduced with permission from Armstrong, K., and McGovern, V. J.: *Tr. Ophth. Soc. Australia* 15: 110-121, 1955; Sydney, Australia, Australasian Medical Publishing Company Limited.

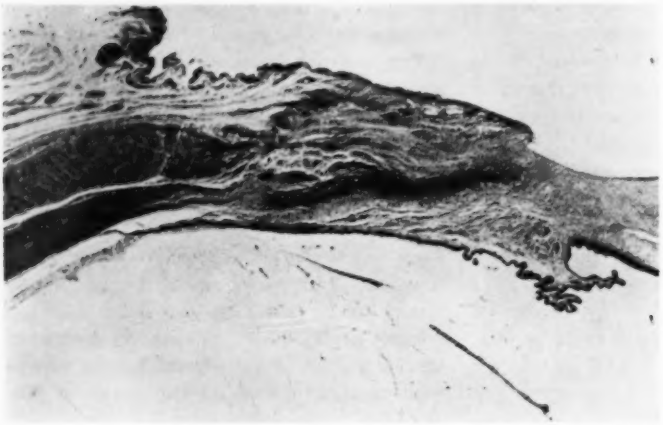

Fig. 7. — Involvement of the anterior portion of fascia lata graft by necrotizing process of scleromalacia several months after original operation. Reproduced with permission from Armstrong, K., and McGovern, V. J.: *Tr. Ophth. Soc. Australia* 15:110-121, 1955; Sydney, Australia, Australasian Medical Publishing Company Limited.

of sharp forceps on one edge of the first graft had damaged it so that a recurrence of the disease occurred in this location. In looking at his photomicrographs, it appeared to me that the graft itself was susceptible to the scleromalacia process (Fig. 7). In my case, a very limited recurrence appeared in the fourth postoperative month, but there was no further change thereafter. It is reasonable to expect that a tissue which is histiologically very similar to sclera might suffer some of its maladies. I believe that both my case and that of Armstrong and McGovern proved this point.

With respect to surgical technique, there were some differences in detail in Armstrong's approach and mine. He dissected the conjunctiva free at the limbus and then carried the posterior edge of the graft backward on long needles, securing the graft by mattress sutures through the lids. In mine, dissection was started almost at the fornix and carried forward. The graft was sutured to the tendinous insertions of the four recti muscles and to the sclera itself.

Conclusions

One may conclude that certain surgical procedures in the treatment of scleromalacia perforations are justified. Enucleation as a primary procedure should not be undertaken. For a small isolated perforation at the limbus an iridectomy and then the use of a conjunctival flap should be employed. For a small isolated scleral perforation the use of a trephine to circumscribe the lesion and replacement of the defect with the donor scleral button is indicated. With a large irregular perforation involving a large section of the globe reinforcement of the sclera by means of a fascia lata graft placed under the conjunctiva offers encouraging possibilities.

33 Mulberry St. (5).

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Cystic Degeneration of the Meibomian Glands

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Relatively little attention has been given to the histopathologic alterations of the Meibomian glands, despite their functional importance and recognized participation in a large group of ocular disorders. Even this limited consideration has been focused on the tumors that may arise from these unique glandular structures, and very little emphasis has been given to the response of the Meibomian glands to obstruction by natural disease or surgical manipulation.

An example of Meibomian cyst was described as early as 1875 by De Vincentiis,[1] and several subsequent reports of Meibomian gland obstruction and consequent cyst formation have appeared.[2-10] In general, these papers present isolated glandular cysts of variable size or refer to Meibomian gland obstruction and cyst formation secondary to trachomatous cicatrization of the lid. A number of recognized ophthalmic textbooks [11-14] mention the occurrence of Meibomian cysts and state that they may also result from congenital maldevelopment of the eyelid, deliberate obliteration of the Meibomian ducts, or eyelid injury, but no comprehensive description is given.

This study was undertaken to determine the pattern of gland reaction following Meibomian obstruction. Consequently, a wide variety of eyelid specimens in the Pathology Department at the Institute of Ophthalmology was reviewed. This selection included neoplastic and inflammatory material as well as tarsal biopsies and a number of clinically normal eyelids. From this survey a distinct entity emerged and certain practical clinical and surgical conclusions became evident. However, interpretations pertaining to Meibomian gland obstruction must be made against a background of normal Meibomian gland development, anatomy, and physiology.

The Meibomian glands appear in the fourth month (80 mm. stage) of intrauterine life as an ectodermal ingrowth from the posterior portion of the fused lid margins.[15] They form a single row of parallel vertically arranged glands occupying the tarsal plate of both the upper and lower lid. Duke-Elder [14] states that there are 30 to 40 glands in the upper lid and 20 to 30 in the lower. Each gland is composed of a central linear duct which emerges on the lid margin between the intermarginal sulcus and the posterior border of the lid margin. Into the sides of this central tube open as many as 30 or 40 small ducts connecting with rounded simple or branched alveoli (Fig. 1). The main duct of the gland is lined by stratified squamous epithelium that is up to six cell layers in thickness. The secretory acini or alveoli contain a basement membrane separating the tarsal supporting tissues from the glandular elements. Lining the periphery of each acinus is a single layer of flat undifferentiated cells. As these cells mature, they move centrally and increase in size. In the center of the acinus, the larger fully developed cells are compressed against one another, assume a polyhedral shape, and contain many fat droplets (Fig. 2). This lipid is responsible for the characteristic yellow color of Meibomian glands and is disclosed histologically by special fat stains or revealed by the coarse vacuoles that remain in the tissue specimen after fat dissolution. Culmination of the secretory

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From the Institute of Ophthalmology of Presbyterian Hospital, New York, and the Armed Forces Institute of Pathology, Washington, D. C. This study was supported in part by a Special Clinical Traineeship awarded by the National Institute of Neurological Diseases and Blindness.

Fig. 1.—Normal Meibomian gland histology. Many secretory acini are connected with each central duct. Hematoxylin and eosin; × 65.

Fig. 2.—Normal Meibomian gland histology. The secretory acini are composed of a basement membrane, a peripheral layer of undifferentiated cells, and a central cluster of maturing sebaceous elements. Hematoxylin and eosin; × 335.

process occurs when the nuclei of the large central cells shrink and degenerate and the cells break down—a holocrine form of secretion—to release a mixture of cell remnants, fat, fatty acids, and cholesterol. The secretory cells are replaced to some extent by mitosis of undifferentiated cells in the periphery of the acinus but principally by the mitosis of duct cells which migrate into the secretory alveolus and mature in the pattern characteristic of sebaceous elements.[16-19]

The sebaceous secretion is carried along the Meibomian duct to the lid margin, where it forms a waxy barrier to prevent the overflow of tears and contributes to the watertight seal of the closed eyelids. This waxy barrier separates the dry and wet lid segments and coincides with the mucocutaneous junction of the lid margin. This junction between skin and mucosa lies at the posterior margin of the Meibomian duct orifice. Here the keratin and eleidin layers of the skin end very suddenly and give way to epithelium composed of about five layers of nucleated, nonkeratinized squamous cells (Fig. 3).

After this introduction resumé of normal gland anatomy, cystic degeneration of the Meibomian glands may be considered. To be unequivocally accepted as cystic degeneration resulting from Meibomian gland obstruction, the lesions must arise in the Meibomian glands, an area of obstruction must be established, and the alterations must be true cysts. By definition, a cyst is an epithelial-lined space filled with the products of epithelial or glandular activity. Gland obstruction may be evident in the histologic specimen or noted by direct inspection of the tissue at the time of surgery. The origin of these cysts from Meibomian glands may be affirmed by demonstrating direct continuity between gland and cyst or conspicuous proximity between gland and cyst in the sharply demarcated tarsal portion of the lid. In this report, the examples of cystic Meibomian degeneration related to neoplastic disease of the lid and to eyelid surgery fulfill these basic qualifications.

Considering first the gland obstruction produced by neoplasm, a particularly clear example of cystic Meibomian degeneration develops in the gland segments adjacent to or proximal to a Meibomian gland carcinoma. At an early stage, this tumor obstructs the gland lumen and retained secretions accumulate. This accumulation results in a distention or ballooning out of the Meibomian duct with little change in the stratified duct epithelium (Fig. 4). The secretory acini also participate in this enlargement and form irregularly round spaces arranged in the linear fashion characteristic of Mei-

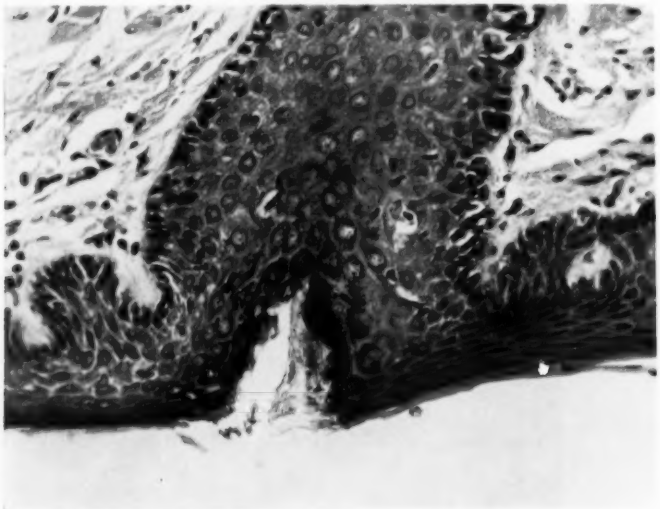

Fig. 3.—Normal mucocutaneous junction on the eyelid margin. Keratinized epithelium of the skin is anterior to the Meibomian duct orifice, and nonkeratinized mucosa is posterior to the gland. Hematoxylin and eosin; reduced about 10% from mag. × 310.

Fig. 4.—Meibomian cystic degeneration adjacent to a Meibomian gland carcinoma. Retained secretions greatly distend the central Meibomian duct. Hematoxylin and eosin; × 54.

Fig. 5.—Meibomian cystic degeneration. The secretory acini are expanded to form irregularly round spaces arranged in the linear fashion characteristic of Meibomian anatomy. Many of these cystic spaces are lined by two or three layers of small flat cells. Hematoxylin and eosin; × 52.

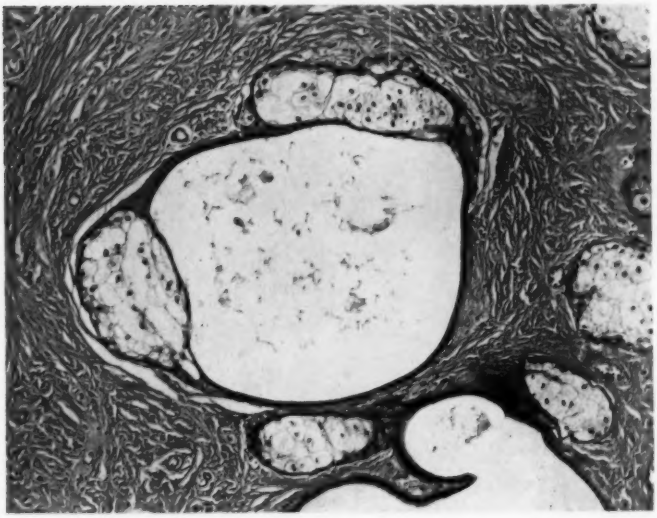

Fig. 6.—Meibomian cystic degeneration. In some cystic acini, small groups of lining cells may show enlargement and even progress to mature sebaceous differentiation. Hematoxylin and eosin; reduced about 10% from mag. × 120.

bomian gland anatomy. The advanced or fully developed cysts are lined by two or three layers of small flat cells very similar in appearance to the undifferentiated cells at the periphery of the normal acini (Fig. 5). In other cystic spaces small groups of lining cells may show enlargement and abortive differentiation or even progress to maturity (Fig. 6). A line of compressed cells generally separates these maturing elements from the main cavity of the cyst.

Similar histopathologic alterations may follow other tumors that compress and occlude the Meibomian glands. Cystic Meibomian degeneration is frequently noted adjacent to basal-cell tumors and squamous-cell carcinomas involving the lid margin. Even a small tumor near the mucocutaneous junction can elicit the pattern of duct enlargement and acinus excavation because of proximity to the Meibomian ducts (Fig. 7).

A more comprehensive understanding of the three-dimensional enlargement that follows Meibomian obstruction can be gained from the contrast between a normal gland cut in cross section—that is, perpendicular to its longitudinal axis—and a cystic gland cut in a similar plane. The normal gland has a relatively small duct that is surrounded by a compact cluster of secretory acini. In cross section the degenerated gland shows the same expansion that is evident in its longitudinal axis. However, in both planes of section the cystic spaces are encompassed by firm bundles of tarsal fibrous tissue which appear to limit their expansion.

Essentially comparable to the interruption of Meibomian secretion by naturally occurring neoplastic disease is the Meibomian obstruction that is surgically produced. A number of eyelid operations cut across or occlude the Meibomian passages, but the foremost example of gland obstruction is the intermarginal lid adhesion. This procedure unites a segment of tarsal plate in the upper lid with a corresponding segment of tarsus in the lower lid and assures Meibomian gland obstruction. As a rule, lid adhesions are employed when disease or exophthalmos threatens corneal integrity and the basic disorder is a contraindication to biopsy of the tarsus.

However, in one instance, lid adhesions were placed to relieve the discomfort of a severe bullous keratitis that developed after keratoplasty and cataract extraction. The adhesions were temporarily effective in relieving the distress, but in a few months the pain recurred and vision became negligible, and so enucleation was indicated. Therefore, six months after the lid adhesions were placed, they were divided and the globe was

Fig. 7.—Meibomian cystic degeneration adjacent to a basal-cell tumor. This tumor developed on the lid margin near the mucocutaneous junction. Hematoxylin and eosin; × 48.

removed. At the time of enucleation, a small segment of tarsus corresponding to the site of a lid adhesion was removed from the upper lid.

This biopsy included the upper portion of the tarsus where the levator aponeurosis is attached. In this upper part of the tarsus, the Meibomian glands deviate somewhat from their parallel orientation and, as a consequence, normal and obstructed elements may be very close to one another. Frozen sections stained for fat show dense lipid

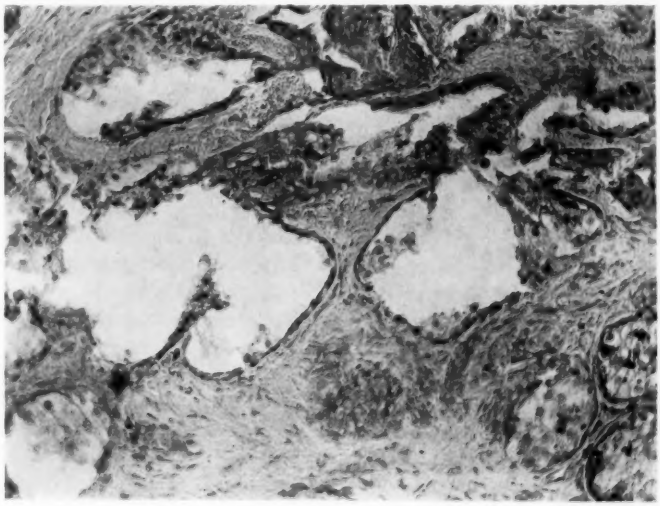

Fig. 8.—Meibomian cystic degeneration and normal Meibomian acini in the tarsus corresponding to the site of an intermarginal lid adhesion. Oil red O; reduced about 10% from mag. × 125.

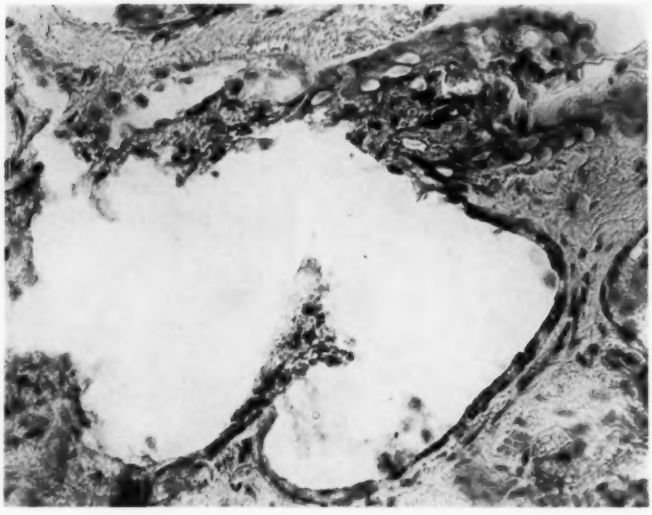

Fig. 9.—Greater magnification of the acini illustrated in Figure 8 indicates that they are lined by small flat cells and contain only a minor amount of stainable lipid. Oil red O; reduced about 10% from mag. × 295.

concentrations in the central zone of the normal Meibomian acini and adjacent distended cystic spaces of the degenerated glands (Fig. 8). Although all glands were occluded simultaneously, some acini show only partial excavation and loss of secreting cells, while other areas reveal more advanced degeneration and are lined by one or two layers of small flat undifferentiated cells (Fig. 9). It seems particularly interesting that special fat stains of these obstructed glands disclose only minor amounts of lipid in the clear cystic spaces. One can only speculate on the nature of the cyst contents and the fate of the lipid once contained in these spaces.

Comment

Comparison between the specimen of surgically induced Meibomian obstruction and the examples of Meibomian occlusion related to neoplastic disease indicates that the glandular reaction is identical. It seems likely that this interference with normal function forces the accumulation of retained secretions. The distended gland spaces tend to enlarge but encounter resistance from the dense fibrous tissue of the tarsus. This tissue resistance and the accumulating secretion elevate intracyst pressure until cell differentiation is inhibited. This inhibition is a gradual process that is associated with evidence of cell compression and abortive maturation in some acini, while others have a thin lining of small undifferentiated cells.

The ultimate size attained by the Meibomian cysts is rather variable and is influenced, in all likelihood, by such factors as the duration of gland occlusion, abruptness of onset, and properties of the tarsal tissues. In general, the cysts are relatively small and remain limited to the tarsal plate. No comprehensive correlation can be made between this histologic description of cystic degeneration and the clinical appearance of the involved tissues, but some of the larger cysts appreciably alter the tarsal architecture and may have been clinically evident. Most of the smaller cystic spaces do not disrupt the tarsal borders and were probably not clinically apparent.

A definite feature of cystic Meibomian degeneration is the absence of an inflammatory process in the adjacent tissues. Only a minimal amount of stainable lipid is apparent in the cystic spaces and the nature of the cyst contents is not known, but certainly this material is well tolerated by the surrounding structures. This complete lack of inflammation clearly separates cystic degeneration from the primarily inflammatory process responsible for the chalazion. By

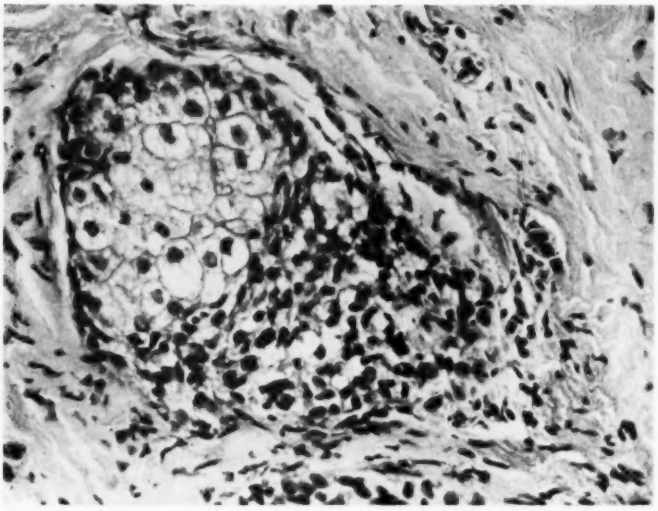

Fig. 10.—Chalazion. In the early stages, leukocytes infiltrate the Meibomian acini and form a cuff in the surrounding tarsus. Hematoxylin and eosin; reduced about 10% from mag. × 360.

way of emphasis, the tissue changes associated with the chalazion may be summarized.

In the earliest stages of a developing chalazion, leukocytes infiltrate the Meibomian acini and form an infiltrative cuff in the surrounding tarsus (Fig. 10). As the inflammatory response becomes more intense, sebaceous cells are destroyed and small empty spaces appear in the acini (Fig. 11). This destruction of Meibomian cells progresses to complete dissolution of the acini, so that their original boundaries are lost in a mass of mononuclear leukocytes, giant cells, necrosis, and organization. This reaction has all the elements of a true granuloma and may undergo clinical resolution or organize to produce a dense mass of fibrous tissue with diffuse ramifications. However, the usual result is a central area of tissue necrosis and liquefaction surrounded by an irregular wall of soft or firm granulation tissue (Fig. 12). Gland obstruction is a very plausible contributing factor in the pathogenesis of chalazia, but the primary factor is, in all likelihood, an infection.

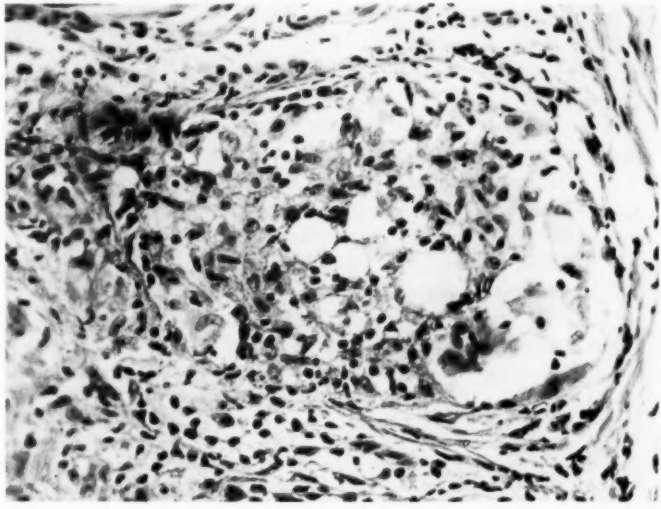

Fig. 11.—Chalazion. The inflammatory reaction may destroy sebaceous cells, and empty spaces appear in the acini. Hematoxylin and eosin; reduced about 10% from mag. × 300.

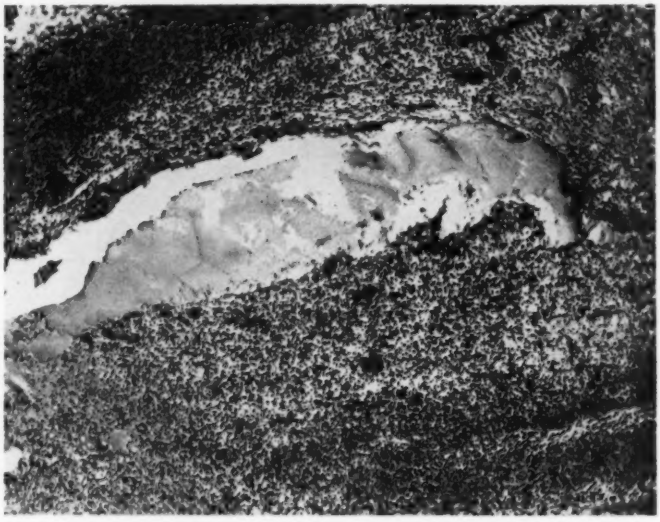

Fig. 12.—Chalazion. The central zone of the inflammatory process has undergone necrosis and liquefaction. Hematoxylin and eosin; reduced about 10% from mag. × 58.

The destructive granulomatous tissue reaction of the chalazion contrasts sharply with the insidious enlargement that follows Meibomian gland obstruction. In separating these two disorders, Meibomian cystic degeneration emerges as a distinct entity of practical significance to the pathologist and to the surgeon. Histologically, the pathologist may consider this cystic expansion as a benign secondary degeneration. When encountered in a specimen, this degeneration prompts a search for the cause of the gland obstruction, but cysts may extend to the edge of the tissue without indicating incomplete excision of the primary disease.

For the surgeon, an understanding of the pattern of Meibomian cystic degeneration explains the liberties that may be taken in operative procedures involving the tarsus. The tarsus is the main supporting structure of the lid, and many plastic and reconstructive procedures alter this structure to achieve their purpose. Examples of tarsal manipulation include the Kuhnt-Szymanowski operation for ectropion, the Streatfield-Snellen procedure for entropion, and the Hughes [20] technique for lid reconstruction. All these operations distort the tarsus and undoubtedly produce a degree of cystic Meibomian degeneration. Of major importance to the surgeon is the realization that these Meibomian gland alterations are confined to the tarsus and do not impair the effectiveness of the surgical maneuver when the glands are uninfected and asepsis is maintained.

Summary

The Meibomian glands undergo a specific form of cystic degeneration when obstructed by natural disease or surgical manipulation. This degeneration is characterized by distention of the Meibomian ducts and enlargement and excavation of the secretory acini. The cystic enlargement is generally limited by the fibrous tissue of the tarsus and does not elicit any inflammatory response. Appreciation of this process is of value in interpreting eyelid pathology and understanding the liberties that may be taken with the tarsus in surgical procedures.

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The Trabecular Endothelium

Its Degeneration in Closure of the Chamber Angle

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The endothelium of the corneoscleral trabeculum is an important part of the filtration apparatus of the human eye.[1-4] Minute details of structure and pathology are valuable, since they may eventually help to understand, prevent, and treat glaucoma.

In this paper a new technique is introduced to demonstrate the trabecular meshwork with its endothelium and the supplying nerve fibers. The examination of the trabeculum of the normal eyes of a small child confirmed the findings of earlier authors. The studies of the trabeculum of eyes with two different types of angle closure following cataract surgery revealed extensive atrophy of the endothelium and changes of the trabeculae. The present paper represents my first report on the pathology of the chamber angle. More papers on this subject are intended.

The reported findings are given with a short clinical description of the cases used for the demonstration. This is necessary, since this paper is composed of findings in human eyes and does not represent the result of repeatable animal experiments.

Method of Histological Examination

The human eyes used for this study were fixed in ammonium bromide formalin (Cajal solution). One half of each eye was imbedded in paraffin, cut in serial sections, and stained with the conventional techniques of routine eye pathology. Tangential sections through the area of the filtration angle were made of the anterior parts of the other halves of the eyes on the freezing microtome. The frozen sections were stained with the threefold and the unreduced methods of the silver carbonate techniques of del Rio Hortega.[5]

All the illustrations of this paper are unretouched photomicrographs.

Report of Histological Findings

Structure of Trabecular Endothelium in Normal Eyes of 2-Month-Old Child and Morphological Differences Between Trabecular and Corneal Endothelium.—The 2-month-old baby girl had been born with a severe congenital heart disease, interventricular and interatrial defects. She died on Feb. 24, 1958, during a surgical attempt to close these defects. The eyes of this baby were chosen for this study, since I primarily wanted to demonstrate the normal endothelium in the trabeculum of a child without any of the degenerative changes which are known to occur with aging.[6]

The macroscopic and histological examination of both eyes of this child revealed the eyes to be normal in all their parts. Both eyes had an anterior chamber of normal depth and an open filtration angle with a well-developed corneoscleral trabeculum and canal of Schlemm. In the tangential sections the trabeculae were found to be delicate and of a rather regularly anastomosing pattern (Figs. 1-3). At high power the bundles of collagen fibers which represent the supporting structure of the trabeculae were well visible and appeared straight and regular. The trabeculae appeared to be completely surrounded by the protoplasm of endothelial cells. The latter structures, however, were very delicate. They were visible in the microscope, but it is hard to

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From the Department of Ophthalmic Surgery and the Laboratory of Neuropathology of the University of Michigan Medical Center.

Fig. 1.—Tangential section through the inner (uveal) part of the normal trabeculum of a 2-month-old child. The endothelium is seen to surround the trabeculae. Some of the endothelial cells are bridging the trabecular spaces (arrow). Threefold method of del Rio Hortega, photomicrograph.

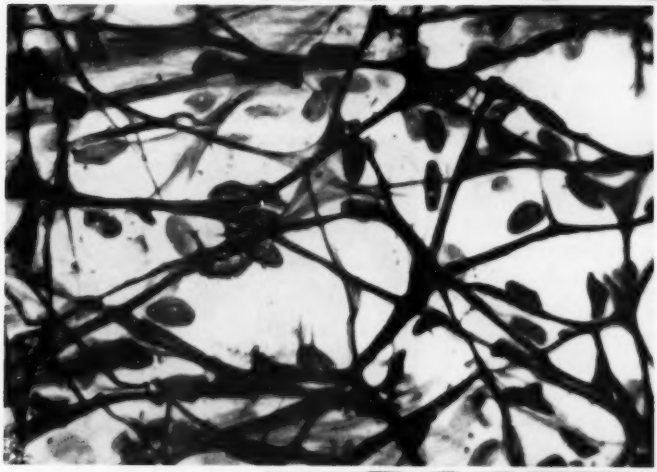


Fig. 2.—Tangential section through the intermediate part of the normal trabeculum of a 2-month-old child. The dense trabecular network and the nuclei of the endothelium are clearly visible. Threefold method of Rio Hortega, photomicrograph.

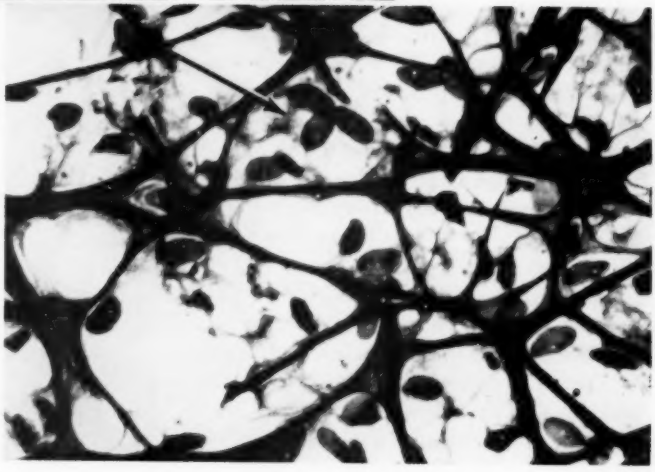


Fig. 3.—Tangential section through the outer (scleral) part of the normal trabeculum of a 2-month-old child. Numerous endothelial cells are seen to surround the trabeculae. Groups of endothelium are bridging the intertrabecular spaces (arrow). Threefold method of del Rio Hortega, photomicrograph.

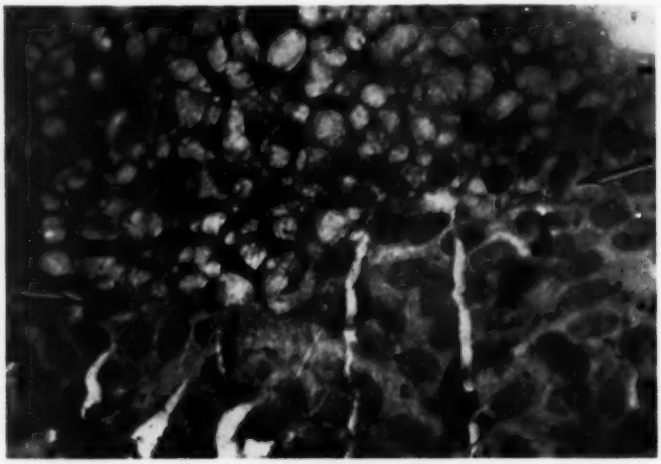
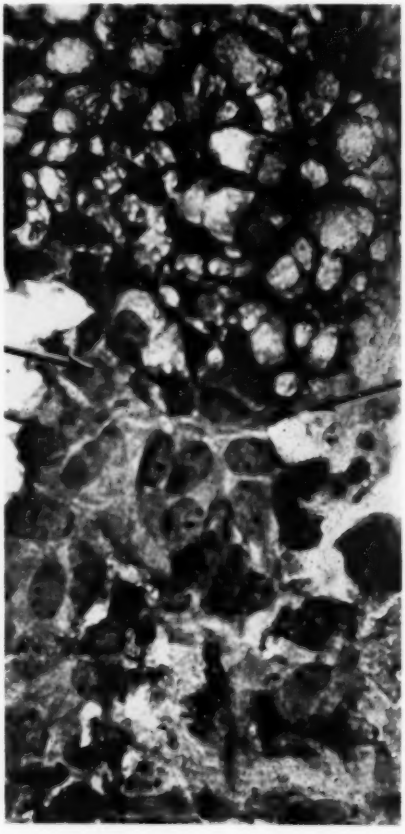


Fig. 4. — Flat section through the corneal endothelium at its limit to the trabecular endothelium of a 2-month-old child. The cells of the corneal endothelium have large intraprotoplasmatic vacuoles (above); the cells of the trabecular endothelium have no vacuoles (below). The limit is indicated by two arrows. Threefold method of del Rio Hortega, photomicrograph.

see their outlines in the photomicrographs. Only in Figures 1 and 3 is some of the endothelial protoplasm visible. The endothelial cells of the trabeculum were found to cover the entire surface of the trabecular meshwork. At many places these cells also bridged the intertrabecular spaces (Figs. 1 and 3). These bridging endothelial cells had no supporting bundles of connective tissue. The nuclei of the trabecular endothelium in this case were rather regularly flat and of an oval shape and had one or two nucleoli.

This case allowed for a histological comparison of the structure of the trabecular endothelium with that of the corneal endothelium. As described above, the trabecular endothelium was well preserved and regular. The corneal endothelium, however, exhibited a very extensive vacuolization of virtually all its cells (Fig. 6). The vacuoles were located in the protoplasm of the endothelial cells. It was interesting to observe that there was a rather distinct limit at the peripheral cornea at Schwalbe's line between the cells of the corneal endothelium which had vacuoles and the cells of the trabecular endothelium which had none (Figs. 4 and 5). The cells of the trabecular and corneal endothelium exhibited some other differences: the nuclei of the corneal endothelium were of a more irregular shape and generally showed a darker stain with silver carbonate; the shape of the cells of the corneal endothelium, however, was more regular and often

Fig. 5.—Another area of a flat section through the limit of corneal and trabecular endothelium (arrows) of a 2-month-old child. The corneal endothelium has intraprotoplasmatic vacuoles and dark-staining, irregular nuclei. The trabecular endothelium has no vacuoles and exhibits oval, pale-stained nuclei with one or two nucleoli. Threefold method of del Rio Hortega, photomicrograph.



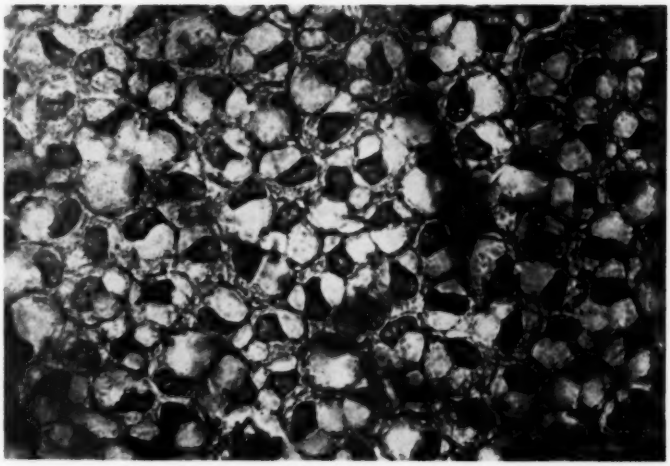


Fig. 6. — Flat section through the corneal endothelium of a 2-month-old child with extensive intraprotoplasmatic vacuolization. Threefold method of del Rio Hortega, photomicrograph.

almost honeycombed in comparison to the more polymorphic trabecular endothelium.

The fact that clear vacuoles are almost regularly found in histological preparations of the corneal endothelium and that such vacuoles are only very rarely found in the endothelium of the trabeculum was first observed and recognized in its significance by Ashton (personal communication). This is an important observation, since it further indicates that the endothelial cells of these two areas must be different in nature and function.

Innervation of Trabecular Endothelium.

A number of excellent papers has been published within recent years on the innervation of the filtration angle.[7-10] The authors of these papers agree that there are numerous nerve fibers in the chamber angle and the trabeculum. Free nerve endings have been demonstrated in the trabeculum.[8-10] Vrabec [8] has been able to show a large nervous end apparatus in a goose eye. However, no special nervous end formations were found in the human trabeculum.

The trabeculum of the eyes of this 2-month-old baby allowed for a demonstration of many branching nerve fibers within the trabeculum. Many of these fibers were obviously just running through the trabeculum and could be seen to enter the peripheral corneal endothelium. Others,

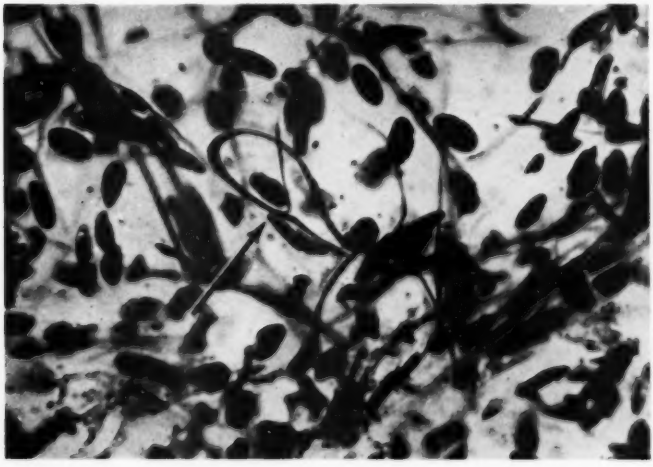


Fig. 7. — A branching loop of a nerve fiber at the posterior part of the uveal trabeculum of a 2-month-old child (arrow). Branches of this nerve are seen on the trabeculae. Unreduced method of del Rio Hortega, photomicrograph.

Fig. 8. — High-power view of the same nerve fiber which is shown in Figure 7.

however, showed frequent branchings and their fibers entered the trabeculum posteriorly. Delicate branches of these nerves were seen to run on the trabeculae and at many places they were seen to be within the endothelial cells. Figures 7 and 9 show

Fig. 9. — Posterior part of the normal trabeculum of a 2-month-old child with a nerve fiber (arrow) which sends nerve branches up into the trabeculum. Unreduced method of del Rio Hortega, photomicrograph.

such branching nerves in the posterior trabeculum. The technique used to stain these nerves (unreduced method) does not stain the collagen fibrils of the trabeculae very well. This explains why the trabecular meshwork in these pictures is not as clearly visible as in Figures 1 or 3, for example. The "terminal" branches of these fibers were seen in the trabecular endothelium. However, they were too delicate to be appreciated in a microphotograph. No special nervous end formations were seen.

The above-described findings on the innervation of the trabeculum and its endothelium are not new. However, they represent a confirmation of some of the beautiful demonstrations of Holland, von Sallmann, and Collins.[9,10]

Trabecular Endothelium in Case of Epithelial Downgrowth Following Cataract Surgery.—This 87-year-old man came to this clinic on July 24, 1958, because of pain and blindness in his left eye. A senile cataract had been removed from this eye about a year before at another hospital. He had never seen much out of the eye operated on, and it had become completely blind about three months previous. One month later the eye became increasingly more painful. At the examination in this clinic, the right eye was found to be normal except for an early senile cataract and some arteriosclerotic vascular changes and drusen (colloid bodies) of the retina. The left eye was totally blind. It was injected and showed photophobia and epiphora. At the slit lamp an extensive bullous keratopathy, corneal edema, and an early band keratopathy were found. Deeper parts of the eye could not be seen. The intraocular pressure was O. D., 15.9; O. S., 10.6 mm. Hg (Schiøtz).

The left eye was enucleated on Aug. 6, 1958. The macroscopic pathological examination revealed the eye to be of normal size and shape. The anterior chamber appeared deep. The iris resembled a thin membrane without much pigment. No lens was found, and the vitreous was liquefied. Microscopically the corneal epithelium was irregular and showed breaks and bullae. The corneal stroma was edematous and showed extensive vascularization and scarring. The corneal endothelium was very atrophic. The whole anterior chamber was occupied by a thin-walled cyst of stratified squamous epithelium (Fig. 10). This cyst was attached to the posterior surface of the cornea, extended into the chamber angle almost up to the trabeculum, and was also in firm contact with the anterior surface of the atrophic iris. The iris and ciliary body showed some infiltration with lymphocytes, plasma cells, and plasmacytoid cells. Remnants of lens substance and lens cap-

Fig. 10.—Epithelial cyst (arrow) in the anterior chamber of an 87-year-old patient. (*a*) Iris; (*b*) cornea. Hematoxylin and eosin, photomicrograph.

Fig. 11. — Tangential section through the trabeculum of an 87-year-old patient with epithelial downgrowth. A part of the epithelial cyst is seen in the left upper cornea. The trabeculum is to the right and down. Threefold method of del Rio Hortega, photomicrograph.

sule were seen behind the iris. The ciliary processes were atrophic. The retina exhibited extensive peripheral cystoid degeneration. The central retina showed a virtually complete loss of the inner retinal layers, nerve fiber, and ganglion-cell layers. The choroid was small and atrophic. The optic nerve showed advanced atrophy. The sclera was normal. The diagnosis after pathological examination was secondary glaucoma caused by downgrowth of corneal epithelium and formation of an epithelial cyst in the anterior chamber after extracapsular cataract surgery, early stage of phthisis bulbi.

Special studies of tangential sections of the trabeculum were done in this eye with the silver carbonate techniques of del Rio Hortega. These sections showed the trabecular meshwork to be somewhat distorted and compressed, but otherwise it was preserved in its normal architecture (Figs. 11 to 13). The trabeculae appeared generally somewhat coarser than those of the small child described above. However, no fragmentation or other destruction of the connective tissue fibrils of the trabeculum were seen. The outstanding finding of this study was the total absence of all the endothelium of the trabeculum in this case

Fig. 12. — High-power view of the inner part of the trabeculum of the patient with epithelial downgrowth seen in Figure 11. The connective tissue structures of the trabeculum are rather well preserved. However, the trabecular endothelium is completely missing. Threefold method of del Rio Hortega, photomicrograph.

Fig. 13. — High-power view of the outer part of the trabeculum of the patient with the epithelial downgrowth seen in Figure 11. The connective tissue structures may be somewhat swollen but are not degenerated. The endothelium is completely missing. Threefold method of del Rio Hortega, photomicrograph.

(Figs. 12 and 13). Not a single endothelial cell was found in all the slides of the trabecular meshwork in this case. Endothelial cells were seen, however, in the canal of Schlemm.

Teng, Paton, and Katzin [2] have reported different types of degenerative changes of the trabeculum, which they observed in primary, open-angle glaucoma. These changes were proliferation of the endothelium, granularity of the collagen, degeneration of the elastic fibers, hyalinization of the endothelium, and distortion and obstruction of the collector channels. Thickening and sclerosing as well as degeneration of the trabeculae and proliferation of the endothelium was also found by Kornzweig, Feldstein, and Schneider [11] in their studies of the trabeculum in primary glaucoma. The finding of a total atrophy of the whole endothelium of the trabeculum as seen in the present eye seems to be new. However, this is not only a new observation, but it also allows for some thoughts about the nutrition of the trabecular endothelium. The trabeculum has no blood vessels. This means that it must be mainly dependent upon the aqueous humor for its nutrition. We therefore explain the total atrophy of the trabecular endothelium in this case by the fact that the epithelial cyst completely obstructed the flow of aqueous humor and with it the nutrition for the trabecular endothelium. This then must have been the direct cause of the atrophy of this endothelium. The fact that there still was endothelium in the canal of Schlemm may be explained by a back-flow of fluid—and with this, nutrition for the endothelial cells —from the side of the aqueous veins into the canal of Schlemm.

Trabecular Endothelium in Case of Flat Anterior Chamber After Cataract Surgery.

This 76-year-old woman came to this clinic on Nov. 18, 1958. She gave a history of having had severe pain in her left eye in 1956. She then went to an oculist in Florida who told her that she had a dislocated and "floating" lens in the left eye. An eye operation was done by the same specialist. However, the vision in the left eye never became better than finger-counting, and the patient was told that a hemorrhage had occurred in her eye.

The examination at this clinic revealed the vision to be O. D., 6/9; O. S., light perception. There was a divergent strabismus O. S. The left eye was red and showed photophobia and tearing. The slit-lamp and funduscopic examination of the right eye revealed some early senile cataract and early arteriosclerotic vascular changes as well as some senile macular degeneration. The right eye was otherwise normal. The

left cornea showed a bullous keratopathy, corneal edema, marginal vascularization, and scarring of the stroma. The anterior chamber was very shallow. The pupil was drawn up and exhibited a white membrane most of which was adherent to the posterior corneal surface. Deeper parts of the eye could not be seen. The intraocular pressure was O. D., 20.2; O. S., 6.2. The clinical diagnosis was senile cataract O. D., senile macular degeneration O. D., aphakia, anterior synechiae and early phthisis bulbi O. S., bullous keratopathy O. S., and divergent strabismus O. S.

The left eye of this patient did not respond to treatment and was therefore enucleated on Nov. 21, 1958. The macroscopic pathological examination revealed this eye to be of normal size and shape. The anterior chamber was extremely shallow. The vitreous was liquefied. The microscopic examination showed the corneal epithelium to be bullous and partly missing. There was chronic episcleral infiltration around the limbus. The filtration angle was completely obstructed by peripheral anterior synechiae and by an old inflammatory membrane in its upper part. The corneal endothelium showed advanced atrophy, and the anterior chamber was extremely shallow. The iris was found to be bound down to a dense cyclitic membrane which contained remnants of lens and lens capsule. There was dense infiltration with lymphocytes, plasma cells, Russell bodies, and macrophages. The ciliary body and the choroid were also atrophic and showed chronic infiltration. The retina exhibited an extensive atrophy mainly of its inner layers. The optic nerve was atrophic. The pathological diagnosis was complete angle closure and chronic nongranulomatous uveitis after extracapsular cataract surgery.

Special stains of the obstructed trabeculum with the Hortega methods were done in tangential sections of the filtration angle. These slides revealed the trabeculum to be somewhat distorted and compressed. The trabeculae also appeared much coarser than they normally do. However, the normal arrangement and structure could still be well recognized (Fig. 14). Schlemm's canal was open. The connective tissue fiber bundles of the outer scleral layers of the trabeculae showed some very extensive thickening and a definite fragmentation of their fibers (Figs. 15 and 16). Virtually no fragmentation of fibers was found in the inner uveal parts of the trabeculum. In this case, however, endothelial cells were found all through the trabeculum. These cells were very much decreased in number and had lost their normal arrangement around the trabeculae. They now represented rather globular elements with irreg-

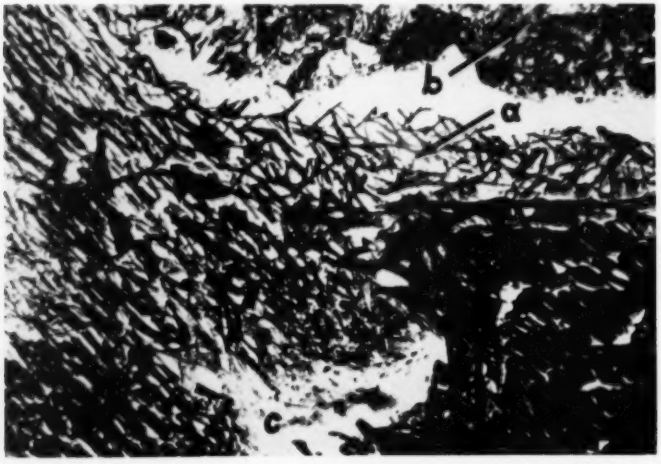


Fig. 14. — Low-power view of the trabeculum (*a*), the iris (*b*), and Schlemm's canal (*c*) in the eye with angle closure of a 76-year-old patient. It can be recognized that the inner part of the trabeculum (above) is rather well preserved. The outer part of the trabeculum (below) shows swelling and degeneration. Threefold method of del Rio Hortega, photomicrograph.

Fig. 15. — Area of the intermediate part of the trabeculum of the patient seen in Figure 14 at high power. The trabeculae are swollen. The endothelial cells are reduced in number and degenerated (arrows). Threefold method of del Rio Hortega, photomicrograph.

ular nuclei many of which appeared swollen (Fig. 15).

The trabeculum of this eye with a flat anterior chamber after cataract surgery showed extensive atrophy and degeneration of its endothelium. However, this was by far not as advanced as in the case with the epithelial cyst. The case with the shallow chamber after cataract surgery, on the other side, had very extensive swelling and fragmentation of the connective tissue fibers of some trabeculae. This was not found in the case with the epithelial downgrowth. The swelling and fragmentation of the trabecular fibers in this case is of special interest, since these changes seem to be much like those described by Teng, Paton, and Katzin [2] as "granularity of the collagen" in the trabeculae in primary open-angle glaucoma. It is not yet understood why such collagen changes were only found in my third case and not in the second.

Studies of more eyes with different types of glaucoma have already shown that the pathology of the trabeculum in this condition as well as in senescence is very complex and not easily understood. In concluding, I would therefore like to emphasize that it is not the purpose of the paper to give a description of the typical

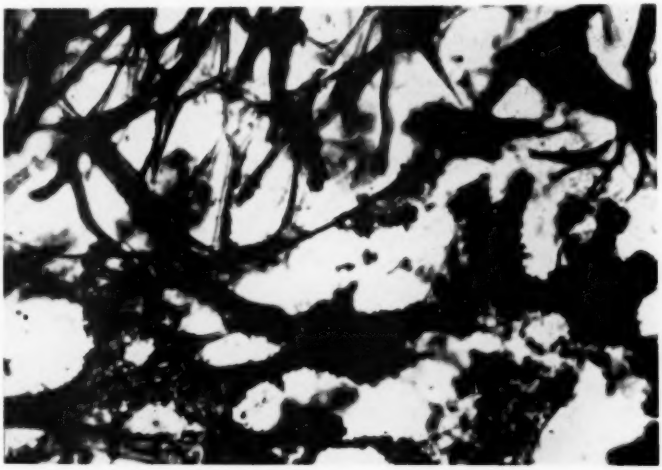


Fig. 16. — Area of the outer part of the trabeculum of the patient with angle closure seen in Figure 14 at higher power. The trabeculae of this area show extensive swelling and fragmentation of their collagen fibers. Threefold method of del Rio Hortega, photomicrograph.

pathology of the trabeculum in secondary angle closure. The main purpose is to show that the silver carbonate techniques are well suited for a demonstration of the elements of the human trabeculum under normal and pathological conditions. It is furthermore of some importance to publish the extensive atrophy of the trabecular endothelium in the two reported cases, which seems to be a new observation. I hope that these findings may later fit in with the results of the studies of intercellar substances in the trabeculum (mucopolysaccharides) which were recently demonstrated by Zimmerman.[12]

Summary

The trabecular endothelium of the eyes of a 2-month-old child was demonstrated with the silver carbonate techniques of del Rio Hortega. Special attention was given to the morphological differences between the trabecular and the corneal endothelium and to the nerve supply of the trabecular endothelium.

The changes of the trabeculum in two cases of angle-closure glaucoma after cataract surgery were studied. A total atrophy of the trabecular endothelium was found in a case of an epithelial cyst in the anterior chamber. Some atrophy of the endothelium and distinct fragmentation of the collagen fibers of the trabeculum were observed in a case of flat anterior chamber.

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The Capacity of the Outflow Channels and the Volume of the Anterior Chamber

JULIUS KESSLER, M.D., New York

The constant relation between the capacity of the outflow channels from the anterior chamber and the volume of the anterior chamber has attracted considerable attention and has aroused some speculation. In order to analyze this relation it seems advisable to consider factors responsible for the volume of the anterior chamber and their influence on this relation.

The volume of the anterior chamber depends on the size of the eye, especially on the size of the anterior segment of the eye; on the position of the diaphragm of the eye, and on the form and the size of the structures which form the diaphragm.

The relation of the capacity of the outflow channels and the volume of the anterior chamber has been found to be reasonably constant in the eyes of different species of various sizes, and this constancy has been suggested as a possible reason for the constancy of composition of aqueous humor.[1]

In this respect, it should be considered that the steady-state concentration of substances in aqueous humor is not dependent on the volume of the anterior chamber. With a given rate of flow and a given rate of entrance of substances, the same steady-state concentration is reached in any volume of the anterior chamber.

In the steady state the sum of all changes of concentration is equal to zero.

$$k_f \cdot (C_\pi - C_a\infty) + k_d \cdot (C_p - C_a\infty) = 0;$$

$$C_a\infty = \frac{k_f \cdot C\pi + k_d \cdot C_p}{k_f + k_d}.$$

A change of volume of the anterior chamber changes both constants by the same factor without altering $C_a\infty$. An analogous reasoning applies to the posterior chamber.

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We can expect that the capacity of the outflow channels is in a rather constant relation to the size of the structures responsible for aqueous humor formation. We shall also not be surprised to find some correlation between the capacity of the outflow channels, the size of the structures responsible for aqueous humor formation, the volume of the anterior chamber of the eye, and the size of the segment of the eye in which they all are located.

In human eyes a lower capacity of the outflow channels has not been established in small hyperopic eyes, while there are some indications for a greater capacity in larger myopic eyes.

Alterations in capacity of outflow with change of position of the diaphragm of the eye have been evident from experiments of Pristley Smith and have been studied recently by J. François[2-4] and B. Becker.[1] Changes in the outflow channels due to a mechanical effect of change of traction by the diaphragm have been suggested as a plausible explanation.

The importance of this factor can be assumed where changes of position of the diaphragm actually occur. Data concerning the capacity of the outflow channels of average-sized eyes with different depth of the anterior chamber and of the same age are not available at this time for an evaluation of the importance of this factor.

The depth of the anterior chamber also depends on the properties of the structures which form the diaphragm. There is no evidence that changes in size or form of these affect the outflow, except by closure of the angle.

The depth of the anterior chamber decreases progressively with age due to increase of the size of the lens. The average decrease in depth is slightly more than half of the average increase of thickness of the lens, and it can be assumed, therefore, that the position of the lens remains essentially unchanged. There is no reason to assume that this decrease of depth of the anterior chamber is accompanied by a significant decrease of outflow due to the change of position of the diaphragm.

On the other hand, a change of the capacity of the outflow channels should cause a change in the opposite sense of the volume of the anterior chamber, so that an increase of the volume of the anterior chamber would occur with a decrease of the capacity of outflow. A mechanism of this kind could be construed as active in homeostasis of the intraocular pressure, reduced capacity of outflow causing posterior displacement of the diaphragm with increase of outflow.

Significant changes of this kind by drug-induced or pathological changes in the natural outflow channels have not been observed. Only considerably larger alterations of outflow or inflow anteriorly or posteriorly to the diaphragm cause significant changes in the position of the diaphragm.

In the individual eye the depth of the anterior chamber is a rather constant characteristic, changing only very slowly with age. This change is mainly due to increase in thickness of the lens and is due slightly, if at all, to a change of position of the diaphragm of the eye. Even in older eyes with shallow anterior chambers and proneness to closure of the angle there is usually a large lens in a small eye and a large capacity of outflow, except for the effects of angle closure, without any evidence of influence of the mechanism connected with the position of the diaphragm.

It has been stated that tonography is of little value unless the depth of the anterior chamber is considered.[4] As far as clinical tonography is concerned, it is rarely done in eyes with changing depth of the anterior chamber, where the depth of the anterior chamber has to be considered. In most eyes the depth of the anterior chamber is rather constant, and the capacity of outflow of the eye, with the depth of the anterior chamber as it is, is all we want to know.

An effect of the change of position of the diaphragm on the capacity of the outflow channels can be assumed in conditions where changes in position of the diaphragm actually occur. It may be misleading to assume that the mechanism is effective in all differences of anterior chamber depth.

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Prevention of Ocular Trauma During Electroretinography

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In the past eight years somewhat over 3,000 patients have been examined with the electroretinogram in our department. In this period of time there have been two instances of corneal burn due to electrical energy from the recording device being fed into the patient. In neither of these instances was there any permanent damage done, but considerable discomfort on the part of the patient and concern on the part of the examiner was engendered.

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Department of Electrophysiology, New York Eye and Ear Infirmary.

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In an attempt to eliminate, as much as possible, this type of accident, a study of the possible sources of such technical failures was begun and a search for a means of prevention of repetition. The electrical circuit normally in use for clinical electroretinography is shown in Figure 1*A*. The patient, who is grounded, is connected by way of a contact-lens electrode to the input of an amplifier. This amplifier develops within it "stray capacities" in its condensers, but these are harmlessly disposed of by grounding the amplifier system.

If, however, as shown in Figure 1*B*, the grounding connection of the amplifier and recording system is loose or broken, the capacities of the system will discharge through the contact lens and, via the patient,

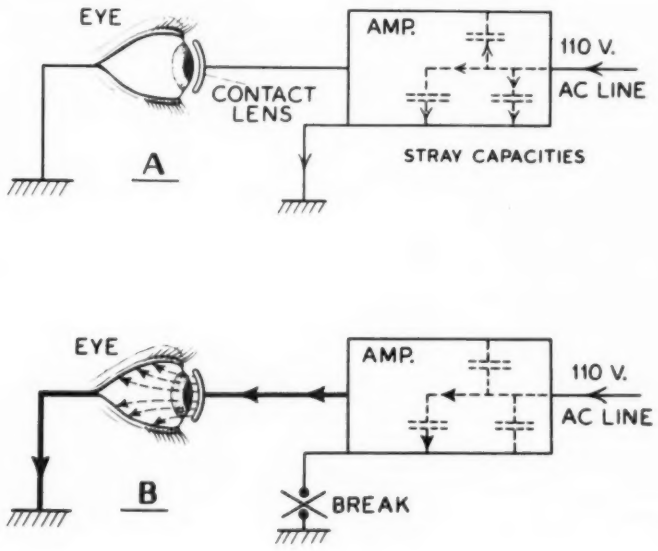


Fig. 1. — *A*, normal ERG circuit, showing dissipation of stray potentials developed in the amplifier to ground. *B*, interruption of grounding circuit of amplifier, with resultant passage of current through the eye.

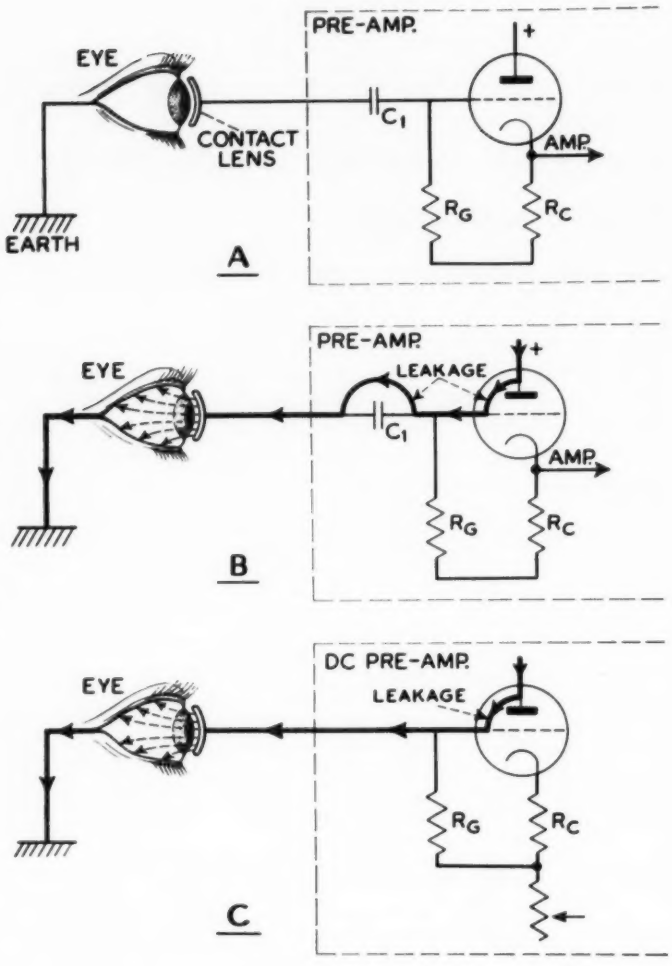


Fig. 2.—*A*, normal input circuit of a condenser coupled amplifier, showing condenser C_1 connecting the contact lens to the grid of the input tube. *B*, failure of condenser and tube, allowing passage of current from the anode of the tube into the eye. *C*, direct coupled amplifier circuit, showing failure of the tube, allowing direct passage of current into the eye.

will seek and find ground potential. The passage of this current through the eye will cause a burn.

Figure 2 demonstrates another type of failure, which we have experienced. The usual condenser-coupled input, through C_1, of the lead from the patient to a cathode-follower preamplifier circuit is shown (*A*). This is the type of circuit almost universally used in clinical electroretinography.

Figure 2*B* shows the cause of one of our corneal burns. Here a dual failure, involving the input condenser which leaked and a tube failure, involving a short circuit between the anode and the grid, allowed leakage of the anode potential, which is about 180 volts, into the patient. Another type of amplifier, using direct coupling, is shown (*C*) to demonstrate how a single failure in the input tube will cause the same leakage.

In order to avoid repetition of the mishaps we have devised a fused circuit for our work. This simple device, shown in Figure 3, is a 2 ma. fuse in a holder which is inserted between the patient and the amplifier input box. Since this fuse will burn out

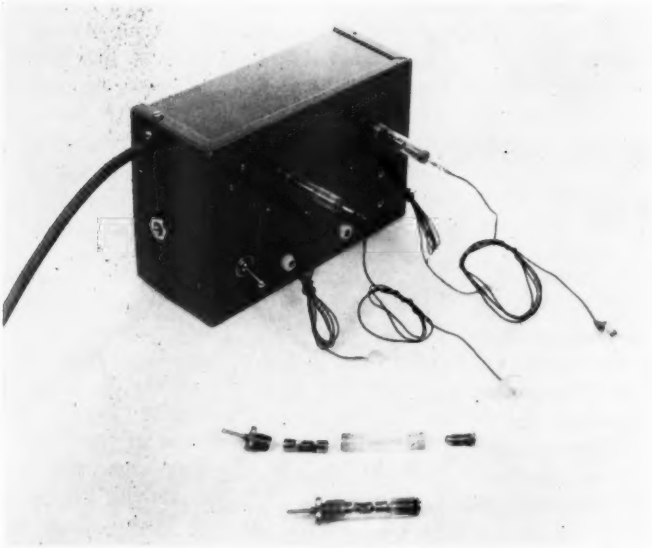


Fig. 3. — Fuse holder assembled (foreground), disassembled (middle), and in place between the amplifier input and the contact lens (top).

upon the occurrence of any current which might possibly cause damage, the patient is protected. We strongly urge the incorporation of a fuse in all electroretinogram circuitry and in electromyography.

880 5th Ave. (21).

A New Retraction Forceps

RALPH SIEGEL, M.D., Perth Amboy, N. J.

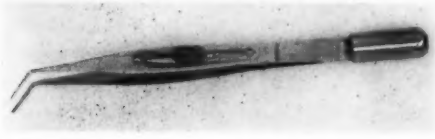
This angulated, locked, fixation forceps weighted at the handle end is used to grasp the conjunctiva and episcleral tissue just outside the limbus for retraction of the bulb during a strabismus operation.

The need for such a self-retaining, bulb-retracting forceps is apparent to ophthalmic surgeons who in the smaller communities, of necessity, must operate alone or with a nurse assistant. This forceps eliminates the use of a muscle hook or a Lester forceps by an assistant to retract the bulb in making the conjunctival incision.

The weighted handle is angulated at 11 mm. from the tip to 120 degrees (Fig. 1).

Submitted for publication Dec. 11, 1958.

Fig. 1.—A new retraction forceps.



The jaws end in teeth which are strong and sharp. They are 1.0 mm. long, one on one side and two on the other, accurately fitting into each other when the instrument * is closed. The angulation is to clear the cornea with the weighted handle resting at the temple (Fig. 2). The handle weighs 6 gm. There is a narrowing in the handle for the clipping on of additional weights should they be desired.

121 Market St.

* Manufactured by Matalene Surgical Instrument, Inc., 125 E. 46th St., New York 17.

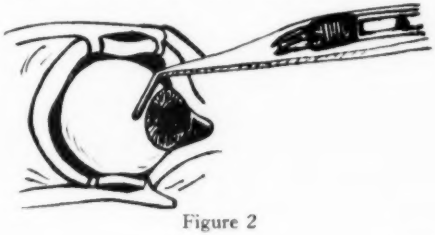


Figure 2

Annual Reviews

Optics and Visual Physiology

ARTHUR LINKSZ, M.D., New York

I. Meetings and a Few Items of Historic Interest

The year 1958 was one of meetings, even of specially organized meetings, to discuss problems of visual physiology. The papers presented at these meetings reveal a considerable shift of emphasis in recent years from so-called psychophysiologic methods to electrophysiologic studies as the means to study visual functions. In fact, one of the first meetings of the year organized in this country was an especial symposium on the electrophysiology of the visual system, held at the National Institutes of Health in Bethesda, Md., Jan. 16 and 17, 1958. Another meeting, a symposium on visual mechanisms, took place Sept. 11 and 12, 1957, at the same Institutes. How significant these meetings and the problems of visual physiology discussed at these meetings were deemed for ophthalmology in general is best illustrated by the fact that our national ophthalmologic journals found it justified and advisable to devote separate additional issues to the dissemination of the material presented at these meetings. The September, 1958, issue of the *American Journal of Ophthalmology* carried as Part II the material of the January meeting; these ARCHIVES published as Part II of their October, 1958, issue the material presented at the other conference. Only the names of the authors and the titles of their papers can be given here—sufficient to impress all students of visual physiology to devote especial interest to the study of these papers.

The contents of the first-mentioned special issue are as follows: "Response Pathways to Electric Stimulation in the Limulus Eye," by L. E. Lipetz; "Responses from the Crayfish Caudal Photoreceptor," by D. Kennedy; "Electric Responses from the Isolated Retinas of Fishes," by E. J. MacNichol Jr. and G. Svaetichin; "Studies on the Functional Organization of the Vertebrate Retina," by H. G. Wagner and M. L. Wolbarsht; "Electric Activity of Toad Retina," by P. Gouras; "Comparison of Spectral Sensitivity at the Eye and the Optic Tectum of the Chicken," by J. C. Armington and G. H. Crampton; "Physical Factors in the Correlation of Electroretinogram Spectral Sensitivity Curves with Visual Pigments," by E. Dodt; "Intraretinal Recording in the Unopened Cat Eye," by K. T. Brown and T. N. Wiesel; "Temporal Periodicities in the Primary Projection System," by W. H. Marshall; "Cortical Unit Responses to Visual Stimuli in Nonanesthetized Cats," by D. H. Hubel; "Analytic Studies of the Electromyogram of Human Extraocular Muscle," by G. M. Breinin; "Familial Electroretinographic and Adaptometric Studies in Retinitis Pigmentosa," by G. Goodman and R. D. Gunkel.

The papers presented at the Symposium on Visual Mechanism included "The Lipoprotein Nature of Rhodopsin," by N. I. Krinsky; "The Behavior of Flash-Illuminated Rhodopsin in Solution," by V. J. Wulff, R. G. Adams, H. Linschitz, and D. Kennedy; "Differentiation, Metabolic Organization, and Viability of the Visual Cell," by W. K. Noell; "Inhibitory Interaction in the Limulus Eye," by H. K. Hartline; "The Human Electroretinogram," by L. A. Riggs; "Present Status of Our Knowledge of Stereoscopic Vision,"

Submitted for publication Feb. 16, 1959.

by K. N. Ogle; "Some Facts and Concepts Regarding the Neurophysiology of the Optic Pathway," by S. H. Bartley; "Color Blindness and Color Theory," by C. H. Graham and Y. Hsia; "On-Responses in the Human Visual System as Inferred from Psychophysical Studies of Rapid-Adaptation," by R. M. Boynton.

The *American Journal of Ophthalmology* has made it a laudable habit of several years to publish the Proceedings of the Association for Research in Ophthalmology, Inc., as a special supernumerary issue. In the past year, this journal did even more for the spreading of basic knowledge in ophthalmology. Just as the Association has grown way beyond its original framework, the *American Journal of Ophthalmology* has also extended the coverage of its activities. First of all, it now publishes under the subeditorship of F. W. Newell advance abstracts not only of the yearly meeting but also of the sectional meetings. In addition, it devoted this year another of its supernumerary issues (July, Pt. 2) to the Association, getting the most important papers of the sectional meetings between separate covers. In this issue there are several papers that need to be mentioned here: "Evaluation of the 'Phosphenator Test'," by L. E. Lipetz; "Correction for the Guessing Bias in the Landolt Ring Test," by J. H. Prince and G. A. Fry; "The Photopic Retinal Receptors of the Typical Achromat," by L. L. Sloan; "Conoid Refracting Surfaces and Conoid Lenses," by D. Volk; "Visual Sensory Units and the Minimal Angle of Resolution," by F. W. Weymouth.

At the meeting of the Western Section of the Association for Research in Ophthalmology (held in November, 1957, but reported in 1958), J. G. Hyde, R. G. Eason, and M. Stevenson showed a motion picture recording eye movement; E. Tamler, A. Jampolsky, and E. Marg gave an electromyographic study of cocontraction in human extraocular muscles, and F. W. Weymouth spoke about spatial perception as a function of retinal stimulation.

A considerable part of the meeting of the Eastern Section was devoted to problems of visual physiology. The papers relating to this subject were by G. Wald and P. K. Brown, on "Human Rhodopsin"; by R. Hubbard and A. Kropf, on "The Mechanism of Bleaching of Rhodopsin"; by T. H. Goldsmith, on "The Visual System of the Honeybee"; by L. L. Sloan, on "Photopic Retinal Receptors of the Typical Achromat"; by M. Iranyi, D. L. Miller, and R. B. Livingston, on "Eye Movements and Visual Pathways in the Chameleon"; by O. Lowenstein and I. S. Loewenfeld, on "Electrically Induced Movements of the Iris Versus Physiologic Reflex Responses"; by J. H. Jacobson and G. F. Gestring, on "The Role of Centrifugal Inhibitory Fibers in the Amplitude of the Electroretinogram," and by R. H. Peckham and W. M. Hart, on "The Interrelations Between Critical Flicker Frequency, the Electroretinogram, Photochemical Mechanisms, and Perceptual Responses."

At the 27th Annual Meeting of the Association for Research in Ophthalmology and the Meeting of the Section on Ophthalmology of the American Medical Association, June 23-26, 1958, in San Francisco, the following papers relating to our subject were read. E. Tamler, A. Jampolsky, and E. Marg, "An Electromyographic Study of Asymetric Convergence"; J. E. Miller, "The Electromyographic Pattern of Saccadic Eye Movements"; A. Chatzinoff, W. Oroshnik, N. Millman, and F. Rosen, "11-CIS Vitamin A in the Prevention of Retinal Rod Degeneration: An Animal Study"; M. G. F. Fuortes, "Electrical Activity of Cells in the Eye of Limulus"; R. Granit and E. Marg, "Conduction Velocities in the Rabbit's Optic Nerve and Their Relationship to Retinal Spikes"; J. H. Jacobson, H. H. Romaine, G. P. Halberg, and G. Stephens, "The Electrical Activity of the Eye During Accommodation"; J. T. Apter, "Changes in Spontaneous and Evoked Potentials on the Electroretinogram Induced by Drugs: Strychnine, Atropine,

LSD-25, Mescaline"; T. J. Martens and K. N. Ogle, "Observations on Accommodative Convergence Especially with Regard to Non-Linear Relationships"; M. Alpern and R. S. Jampel, "The Effect of Topical Application of Certain So-Called Autonomic Drugs on Human Visual Flicker Discrimination"; A. D. Ruedemann Jr. and W. K. Noell, "A Contribution to the Electroretinogram of Retinitis Pigmentosa." The lecture of the invited foreign guest, Prof. G. Karpe, of Stockholm, "Indications for Clinical Electroretinography," was an important event.

Among the papers read at the meeting of the Midwestern Section, the following are to be mentioned: G. H. von Noorden and H. M. Burian, "An Electro-Ophthalmographic Study of the Behavior of the Fixation of Amblyopic Eyes in Light- and Dark-Adapted State"; E. Simonton, "Contralateral Glare Effect on the Fusion Frequency of Flicker"; L. Stein, "Ultraviolet Luminescence of the Anterior Segment of the Eye"; J. T. Schwartz and K. N. Ogle, "On the Depth of Focus of the Human Eye"; G. P. Arnott and M. Armaly, "The Effect of Sympathectomy on Certain Electroretinogram Functions," and J. E. Miller, J. Hartstein, G. Ullett, and L. Johnson, "Preliminary Studies of Photic Driving in Amblyopic and Normal Children."

There was also a Conference on Photoreception on Jan. 31 and Feb. 1, 1958, under the sponsorship of the New York Academy of Sciences in New York. Separate sessions were devoted to photoreceptor structures, visual pigment photochemistry, and electrophysiology. At least the titles of some of the contributed papers should be given. Session I: "Studies of Photoreceptor Structures," by J. Wolken; "Biochemistry and Electrophysiology of Insect Vision," by T. H. Goldsmith; "The Electrical Activity of a Primitive Photoreceptor," by D. Kennedy; "Optics of the Insect Eye," by H. de Vries. Section II: "The Natural History of Visual Pigments," by F. Crescitelli; "Visual Pigments and Environment," by H. J. A. Dartnall; "The Kinetics of Cone Pigments Measured Objectively upon the Living Human Fovea," by W. A. H. Ruston. Session III: "Invertebrate Photoreceptors," by W. H. Miller; "Problems in Visual Cell Physiology," by W. K. Noell; "Human Retinal Responses," by L. A. Riggs; "Analysis of Receptive Fields in the Cat's Retina," by T. Weisel; "What is Behind the Eye?," by W. McCulloch. Of the papers read at the closing session, I want especially to mention "Some Aspects of the Absolute Sensitivity of the Eye," by M. H. Pirenne. (The material presented at the conference was published by the sponsoring Academy and can be purchased by writing to 2 E. 63d St., New York 21.)

The Spring Meeting of the Optical Society of America, March 27-29, 1958, in Washington, D. C., offered (as always) some papers which should interest students of visual physiology. Most of what is called "Optics" by members of this distinguished body is beyond the grasp or interest of ophthalmologists and only makes the equivocal meaning of the word "optics" strikingly apparent. All the invited papers, dealing with such problems as interaction of radiation and matter, control of plant growth by radiation, dual rate moon camera, and spectroscopy of excited gases, have, obviously, nothing much to do with *ops*, the eye, or *opsis*, vision. The same can be said about most of the contributed papers. Even most of the papers which purportedly dealt with "color" were not actually papers of interest to us. There were, however, some that should be, and one will be gratified that the classic psychophysiologic approach to problems of vision, all but abandoned by American ophthalmologic researchers, still finds some devoted cultivators even in America. I want to mention only a few papers. Among those dealing with color vision, the following are of interest: S. M. Newhall, R. W. Burnham, and R. M. Evans, "Effects of Shadowing on Surface-Color Perceptions"; L. Dimmick and R. E. Wienke, "Effect of Luminance Level on the Red-

Green Ratio"; T. N. Cornsweet, H. Fowler, R. G. Rabedeau, R. E. Whalen, and D. R. Williams, "Changes in the Perceived Color of Very Bright Sources"; A. J. Fielding, "Color Temperature and Scotopic Thresholds"; R. W. Burnham, "Comparative Predictions of Color Appearance with a Change from Daylight to Tungsten Adaptation"; H. G. Sperling, "Psychophysical Study of a Case of Congenital Tritanopia."

At one of these sessions one could hear discussion of the following interesting topics: A. M. Nathan, "A Polarization Technique for Improving Visibility in Fog and Haze"; D. E. Spencer, "Fog on Runways" and "Fog on Turnpikes."

Of special interest to us should be a group of papers presented at one of the sessions under the chairmanship of Louise L. Sloan. These were S. S. Stevens and J. C. Stevens, "Dependence of Brightness on Luminance"; K. N. Ogle, "A Note on Stereoscopic Acuity and Observation Distance"; R. W. Brown, "Effect of a Target's Position in an Empty Visual Field on Its Visibility"; F. W. Hebbard, "Variation of Physiological Nystagmus with Convergence"; T. N. Cornsweet, "A New Technique for the Measurement of Eye Movements"; J. Krauskopf, "Analysis of Saccadic Eye Movements During Monocular and Binocular Fixation"; R. E. Wienke, "Refractive Error and Color Vision."

The Annual Meeting of the Optical Society of America (Oct. 9-11, 1958, Detroit) started with an invited paper of Prof. W. D. Wright, of the Imperial College of London, on "Color Standards in Commerce and Industry." The distinguished author remarked that color matches in industry are most frequently judged by the eye and that instrumental color-measuring techniques have in general found little favor. They found it, at least, a debatable question whether instrumentation should replace visual inspection. Another invited speaker, S. H. Land, of Polaroid Corporation, spoke "On the Nature of Color in the Image Situation." The third invited paper, by N. A. Finkelstein, dealt with a rather new and interesting development in optics, called "Fiber Optics" (to which I made some reference in the previous issue of this Review).

The Ives Medal was given to Dr. Dean B. Judd, of the National Bureau of Standards, Washington, D. C., and the material of his acceptance speech, "Some Demonstrations I Have Shown," will, when published *in extenso*, interest all students and especially all teachers of physiologic optics.

Around such an array of distinguished lecturers, there was a crop of contributed papers on color of which I will mention none, since they have only nominal connection with problems of visual physiology. To me all those never-ending efforts (which practically filled up one of the section meetings) of "colorimetric transformation" of particular values from one primary system to the other and all those papers on "Munsell renotations," finally with use of an I. B. M. electronic computer for mechanized conversions, sound devoid of any physiologic significance. Among the papers of interest to us were "Subjective Color Scales and Their Dependence on Adaptation," by D. Jameson and L. M. Hurwich; "Fusion of Intermittent Photic Stimuli," by C. R. Brown; "Effect of Viewing Conditions on Observer Accuracy," by N. D. Miller and V. J. Carpenter; "Effect of the Size of a Complex Display upon Visual Search," by J. M. Enoch, and "Wide Field Aspheric Cataract Lens Series" ("the lens which significantly improves visual acuity for oblique fields of view, is lightweight, and cosmetically attractive"), by J. K. Davis.

The year 1958 will, of course, also be remembered for the XVIII (and centennial) International Congress of Ophthalmology, in Brussels.

The first official *rapport* of this meeting was actually devoted to a chapter of applied visual physiology, orthoptic treatment and pleoptics, with A. Bangerter, T. Keith Lyle, and J. Malbran as chief *rapporteurs*. Electroretinography was the subject of one of the prearranged symposia, and the

names of the opening speakers with the titles of their discussions will be sufficient to indicate the number of people and countries engaged in this relatively new branch of research and the variety of their approaches. J. François offered a general introduction. The speakers and their topics were "Some Clinical Considerations on the Analysis of the Human Electroretinogram," by J. Vanysek; "Techniques for Recording the Human Electroretinogram," by L. A. Riggs; "Universal Photostimulator," by J. François, G. Verriest, and A. De Rouck; "Functional Tests in Clinical Electroretinography," by H. M. Burian; "The Significance of the Electroretinogram for the Clinical Classification of the Different Forms of Hemeralopia," by A. Franceschetti and P. Dieterle; "Some Ocular Affections in the Light of ERG Examination," by S. W. Hamburg; "Flicker Electroretinography," by G. Karpe; "Clinical Results of Cone Electroretinography," by H. E. Henkes. There were 17 participants in the discussion, and some of it was very interesting. Only lack of space prevents me from listing their topics.

Scanning through the material presented at the other symposia, one will note the fertility of physiologic evaluation in a variety of clinical fields. In the Symposium on Glaucoma (it was officially called a Symposium on the Genesis of Functional Symptoms in the Eye with Raised Tension), one finds papers on perimetry (Dubois-Poulssen; Magis and Manjous; Harms), adaptation (Ourgard), electroretinography in glaucoma (François and De Rouck), color vision in glaucoma (François and Verriest), and the visual functions of the glaucomatous eye (Perkins). (In fact, the symposium could very well have been called one on the visual physiology of the eye with raised tension.)

Among the "free" communications there were several (grouped mostly together into one of the afternoon sessions) which here should be mentioned. Casanovas spoke about optotypes which permit the detection of simulation; Cooper and Girling, about problems related to accommodation; myself, about aniseikonia; Vestsmith, about the monocular correction of presbyopia with the use of corneal lenses; Kestenbaum and Moffat, about visual aids; Strampelli, Schreck, Choyce, and J. Barraquer, about anterior chamber lenses.

Another group of these free papers was devoted to disturbances of color vision and other ocular problems of hereditary nature. Sarwar spoke about color vision defects in children, and Franchescetti and associates, about a family of achromates on Fur, a small Danish island. Eccentric fixation as a problem of heredity was discussed by Algan and associates; the disturbances of binocular vision, by Reusch; the mechanism of the development of scotomata in strabismus, by Strzyzewski; after-images, by Aulhorn, and problems of electromyography, by Huber and by Blodi and van Allen.

There was a paper on the practical psychology of vision by Sennewald. Several papers—by Simpson, Gogler, Savin—dealt with visual problems of the automobile driver. In the scientific exhibit of instruments, there was one by Ridley which offered a televised picture of the eyeground, Rotter and Schmidt spoke about the theory and practice of the slit lamp, and Weber explained his method of measuring differences in the fundus with successive stereopictures.

A double issue of *Ophthalmologica*, a volume of some 300 pages, contains papers delivered at the 15th anniversary meeting of the Swiss Ophthalmological Society. The principal subjects of this meeting (hypertension, diabetes) fall outside of the field covered by this Review. Two papers are of interest: one is the report of R. Fessel on 15 years' activities of the pleoptic school in St. Gallen; the other, by F. Frankhauser and T. Schmidt, deals with spatial summation with stationary and moving targets studied by the method of quantitative light-sense perimetry.

The greater part of another issue of *Ophthalmologica* is devoted to papers read

at the May, 1957, meeting of the Netherlands Ophthalmological Society.

An apparatus for light coagulation of the fundus was constructed according to the principles developed by Meyer-Schwickerath in the Physical Laboratory of Utrecht University. The instrument and some clinical cases in which it was used were shown by J. ten Doesschate. M. J. Schweitzer and M. A. Bouman reported on "Differential Threshold Measurement of the Light Reflex of the Human Pupil"; J. ten Doesschate spoke about "Differential Threshold and Firing Probability of the Off-Effect in the Frog Retina," and R. Granit delivered his Donders Medal Lecture on the "Physiological Basis of Flicker Electroretinography as Applied in Clinical Work."

There was an important meeting at the Collège de France in Paris, July 25 to 29, 1958, sponsored by the International Council of Scientific Unions, and called "International Symposium on the Fundamental Mechanisms of the Chromatic Discrimination in Animals and Man," under the chairmanship of Prof. H. Piéron. I can only give the names of the distinguished *rapporteurs:* Dartnall, London; von Frisch, Munich; Galifet, Paris; Hurvich, New York; Le Grand, Paris; Rushton, Cambridge; Stiles, Teddington; Viaud, Strasbourg. The names of the discussants would compose a no less brilliant array: Hurvich, Farnsworth, Riggs, and Westheimer were the participants from the United States. One will anxiously await publication of this Symposium. This was discussion on a high level, not the mathematical swordplay which in most of our meetings figures as contribution to color vision. The report of Professor von Frisch on the color vision of bees must have been the highlight of the meeting. I am especially happy that Professor Hurvich, of New York University, held up the torch of the Heringean Heresy and, from all the preliminary information I have, held it up well.

A useful bibliography of the history of ophthalmology, including the years 1955 and 1956, was prepared by Mr. Charles Snyder,[1] Librarian of the Lucien Howe Library of Ophthalmology, in Boston. This is the second installment of this worthy undertaking, which will surely interest every student of visual physiology. It is hoped that the series will continue.

It should be a pleasure for anyone interested in visual physiology, especially in the history of this doctrine, to read a paper by Rucker,[2] on the history of the concept of semidecussation of the optic nerves in man. The first of the 10 well-selected illustrations is, rightly, that of the great Isaac Newton, as the first published reference to this concept (1709) was his. The last illustration comes from the book of John Taylor and shows the Chevalier's ideas about semidecussation (1738). Ample quotations follow from Vater and Heinicke (1723) and from Wollaston (1824), who rediscovered the half-crossing on clinical evidence. The 50 bibliographic references contain the most important pertinent early publications. Their compilation should in itself be ample reason for thankfulness by every reader.

One of the important events in book publishing in the current year was the reprinting, with comments by experts, of Isaac Newton's papers and letters on natural philosophy (as "science" was called in those days), with the great modern science historian, I. Bernard Cohen,[3] as chief editor. The volume starts with 15 papers on physical optics reproduced as they were published in the *Transactions of the Royal Society of London.* This is a beautiful volume to look at and to read.

All interested in vision will be delighted to read Sir Stewart Duke-Elder's Lister Oration[4] about "The Emergence of Vision in the Animal World." He envisages the emergence of vision in terms of Morgan's theory of "emergent evolution" and of Wundt's theory of "creative synthesis." It unfolds in three stages—motor taxis, perceptual vision, and imaginative vision. "The brain of each of us creates a symbolic representation of the outside world, but this personally created world of symbols is our own and private. . . . To some the painting

of Picasso is more full of meaning than is the Mona Lisa . . ." (One hopes that Sir Stewart is not one of them.)

II. Light and the Retina

O'Brien (1951) devised a model, approximately 70,000 times the size of a foveal cone ellipsoid. The wave length of the radiant energy was similarly magnified to $\lambda = 3.2$ cm. The same type model receptor was used by Enoch and Fry[5] to extend the scope of O'Brien's work. They studied the sensitivity of their "receptor" to different positions in the diffraction pattern into which the stimulating radiation is resolved, also the effects of varying the wave length of the radiation and the orientation of the receptor. (Naturally, such investigations offer analogies only—but as such these are extremely interesting.)

Dillon and Zegers[6] determined absolute foveal luminosity thresholds for every 10-mμ interval from 400 to 700 mμ for five observers, and it is a fine and formidable piece of work. (Such reevaluations of "classic" data with new techniques of measurement and statistics are always important.) They used 1-degree test fields and found that for the 550 mμ sample average corneal threshold is 14,600 quanta. This at the level of the retina gives 8,000 quanta or (assuming that their test field of 1 degree covered 12,000 foveal cones) 2 quanta for every 3 cones. Assuming an absorption factor of 10%, this would give 2 quanta for 30 cones or 1 quantum for every 15 cones. Taking Polyak's values, according to which approximately 12 cones are connected to a single *e* or *f* bipolar, the ultimate threshold value is 1 quantum for 1 bipolar. Analyzing either their "foveal" or their "retinal" curves, one sees that they are definitely not of uniform curvature but reveal some humps and dips. Such "quantitative" details, of course, contain much that is of conjectural nature, since they are the outcome of multiplications with corrective coefficients of absorption and, depending on what type correction one uses, one can get a dip or a hump at the same spectrum locus. This is especially noticeable in the range around 480 mμ, where one gets maximum sensitivity in the "retinal" (i. e., adjusted) curves and a downward slope in the "foveal" curves.

In contradistinction to these data, those of Luria[7] deal with the absolute threshold for a composite illuminance sample and an extremely wide field. His test illumination covered a 100-degree area and had a color temperature of 2,050 K. He found a threshold value of 2.35 log $\mu\mu$L. He thinks this threshold value would even further decrease with increasing stimulus area and arrive at an absolute minimum value when the limits of the visual field are reached. He also found the threshold to be dependent on the age of the person and the size of the pupil.

An outstanding piece of research, by Enoch,[8] clarified many of the more obscure aspects of the retinal response to light entering different parts of the pupil—among them especially Troland's additivity principle and the much better known Stiles-Crawford effect. He devised several instruments to carry out this study. He feels that besides the Stiles-Crawford effect, it is the blurr of the retinal image, caused by aberrations, which influences the summated response. His experiments show that this effect is not dependent on the Maxwellian distribution of light in the eye (the focusing of the beam into the entrance pupil of the eye) but is also manifest under ordinary viewing conditions (when the light beam is focused on the retina).

DeMott and Boynton[9,10] published two interesting papers on the retinal distribution and the sources of entoptic stray light. To determine its distribution they used freshly excised steer eyes (also some living cat eyes and excised pig and sheep eyes). What they actually measured was the illuminance distribution across the retina resulting from a parallel beam of light incident upon the cornea. The determination was made through a small opening in the back of the eye with use of a photomultiplier tube. Pupillary diameter had no effect on the

distribution. Some random sampling from their wealth of data reveals that if relative illuminance at 0 degrees (the site of the theoretical image) is designated as 100% one can still find 0.15% at 7 degrees and 0.0014% at 50 degrees from that spot. One also learns that of the total flux which supposedly concentrates in an image point actually only 15% are contained within the ½-degree square which contains this image. It is also interesting that light of different wave lengths does not scatter uniformly. As known from psychophysical experiments, blue scatters most.

To determine the sources of the stray light they invented a surely unusual and original technique. They used a freshly removed steer eye, cut off the posterior one-third of it, and, throwing light obliquely through the pupil onto the retina, traced (by a photographic method) the stray light which left the eye through this artificial back window. They found that about 70% of the stray light stems from the cornea; the rest comes mostly from the anterior and posterior surface and the center core of the lens; some, however, also derives from the aqueous.

Two papers by Dzn,[11] from the Phillips Research Laboratories in the Netherlands, carry the title "Research into the Dynamic Nature of the Human Fovea→Cortex Systems with Intermittent and Modulated Light." The papers are probably interesting and informative to those familiar with the language of communication engineers. I dutifully record their titles for the benefit of those who might be equipped to understand them. Unfortunately, I could not follow the exposition.

Hillmann[12] measured the absolute visual threshold of the human fovea. Stimulus areas were varied from one minute to 1 degree, durations from 1.8 to 48.0 msec. As exposure time increased, threshold intensity decreased in good agreement with the Bunsen-Roscoe law. The area-threshold function did not agree, however, with Ricco's law.

Blough[13] studied differential brightness sensitivity at the fovea and at retinal loci of increasing eccentricity, varying the background brightness from 0.0001 to 10 ft-L. He found that as retinal eccentricity increased, the ratio between ΔB (added brightness) and B (background brightness) increased with it. When brightnesses were great ΔB increased with eccentricity, when brightnesses were low the opposite was observed. This behavior obviously mirrors the activity of two different kinds of receptors.

Zigler and Wolf[14] studied uniocular and binocular scotopic sensitivity presenting a 2-degree-square test field for 0.04 seconds in a Crozier-Holway visual discriminometer in both vertical and horizontal meridians from 0 degrees up to 30 degrees eccentricity in steps of 2.5 degrees. They arrived at sensitivity profiles which show that the binocular thresholds in the vertical meridian are about 0.25 log units lower than either eye's uniocular thresholds—a proof for a true summation effect. In the horizontal meridian things are more complicated. Here the lack of sensitivity in an area of the temporal field of one eye (which corresponds with the blind-spot) is compensated by an area of very high sensitivity in the nasal field of the other eye. In binocular vision, the threshold in the areas corresponding to the respective blind-spots is still lower. The maximum sensitivity is found between 7.5 and 12.5 degrees below the fixation point.

A paper by Kinney[15] contains some (at least to me) entirely new and very significant results. She established spectral sensitivity curves for the retina 10 degrees off center and found that even when intensity was increased to a level of 3.5 to 4 log units above threshold, the curves still retained much of their scotopic shape (though, naturally, relative sensitivity to longer wave lengths did increase as intensities increased, especially beyond the 4 log unit level). This was true for both dark- and light-surround conditions. Even at 5 log units above threshold, the periphery is still more sensi-

tive to short and less sensitive to long wave lengths than the fovea. The ability of the eye to discriminate brightness differences was greatly improved under the conditions of the light surround.

Frankhauser and Schmidt [16] studied retinal summation (the relationship between the size and intensity of the projected test marks used with the Goldmann perimeter) with both stationary and moving test objects. They found that summation increases from the center of the visual field toward the periphery and that it is greater for small than for large test marks.

Bedford and Wyszecki, in two papers,[17,18] deal with changes of discrimination and with the apparent luminosity in normal trichromates depending on variations of the size of test field and of the intensity of retinal illuminance. With use of high intensities they found a definite minimum in the wave-length discrimination curve at 420 mμ. Otherwise, the results with 1-degree field size agreed essentially with those of previous workers. With the smaller field size of 12 min. discrimination did not become poorer. It did with a field size reduced to 1.5 min. Decreasing the light intensity also caused the wave-length discrimination to deteriorate. Keeping to a field size of 12 min. and increasing retinal illuminance from 50 to 500 troland they noted a kind of reverse Purkinje effect, a decrease of the spectral sensitivity to blue relative to red. Going with illuminance in the other direction, from 50 to 7 troland, most observers experience the direct Purkinje effect. With 1.5 min. field size, the reverse Purkinje effect manifested itself at the lowest of the three levels of illuminance at troland. The authors compared the luminosity curves of several observers and found considerable variation. They do not think that a "standard" luminosity curve is a useful concept nor should it be used in any kind of fundamental studies of the visual process.

Dreyer [19] investigated contrast sensitivity (the Fechner fraction) of the central retinal area in light adaptation. His studies suggest that the cones in the fovea are able to cooperate in functional units. The number of cones which cooperate in such units can be put at about 35. Their number is probably dependent on the state of adaptation. Since the random movements of the eye during fixation cover about 10 cone diameters, fixation nystagmus will not interfere with the assessment of the geometric image within individual groups of cones.

Warren and Warren [20] made an interesting analysis of our ability to judge relative brightness. They feel that this judgment is only based on experience, not on some psychophysical law. One judges, in their opinion, the amount of light reflected from objects—an amount which is constantly and regularly changing with the change of distance from a light source. Under experimental conditions which simulated familiar situations, one-quarter of standard luminance was correctly chosen for the effect of doubling the apparent distance from the light source. The same one-quarter luminance was chosen if the observers were asked to judge one-half brightness.

Simultaneous brightness contrast manifests itself in the reduction in brightness of a field of low luminance when a field of very high luminance is brought close to it. One will hardly expect that this reduction in brightness will have the same consequences as "real" reduction of brightness. One will, therefore, not be surprised that unilateral reduction in apparent brightness by a glare source does not cause a Pulfrich effect. This has, in fact, been found by Diamond.[21]

Laue [22] produced dark-adaptation curves in normal people, 18 to 95 years old, on the Goldmann-Weekers adaptometer. The conditions of observation were varied as follows: (1) stimulus field 11 degrees in diameter and homogeneous, pupils dilated and undilated; (2) stimulus field of the same size but inhomogeneous (consisting of dark and light stripes of maximum contrast), again pupils both dilated and undilated; (3) stimulation of the total field with pupils artificially dilated. Such studies mainly serve to acquaint a worker with his

own instrument and the development of the most desirable technique. Finally they offer a basis for comparison in pathologic cases.

Wald and Brown [23] studied the behavior of rhodopsin of a number of human eyes within a few hours after enucleation. Human rhodopsin shows maximum absorption in aqueous solution at 493 mμ. This is due to a characteristic human opsin. The retinene is the same 11-*cis* variety found in other species. Regeneration of rhodopsin from retinene and opsin is faster in vitro than in the eye and faster than human dark adaptation. Within the eye the speed is limited by reactions which precede the union of the two substances. Maximum absorption in vivo is at 500 mμ.

Experimenting with light of shorter wave lengths than 700 mμ, Blough (1957) had previously found a dark-adaptation curve of the familiar duplex form in the pigeon's eye. At 700 mμ, he found another deviation, a "hump," an increase of threshold sensitivity after the first plateau. New experiments [24] show that the time of appearance of this dark-adaptation hump depends on preadaptation. Blough suggests that this hump is the sign of rod activity which at a certain point in the course of dark-adaptation inhibits the activity of the cones—a sort of competition between rods and cones already suggested by Granit.

I reported in the previous issue of this Review on Berens' study, "The Retina, Its Role in the Speed of Perception," which appeared in Vol. 1 of "Modern Problems in Ophthalmology." This important essay [25] was reprinted with additions and should be read extensively. The main topics discussed are visual reaction time, perception of movement, target-sighting, speed of vision at night, and speed of vision in relation to high speed. They are all timely topics (we can almost call them vital topics).

Yves Le Grand,[26] the author of the famous French text on physiologic optics, published a paper on the protection of the eyes against ultraviolet. This is a good compilation of data and well worth reading. It is not suited for abstraction. There is a good bibliography, and one of its features (rather unusual in French publications) is the preponderance of Anglo-American references.

Berens and Crouch [27] try to answer the often-heard question, "Is fluorescent lighting injurious to the eyes?" They found that it has only one questionable feature, namely, that "visual acuity is poorer in daylight (blue) fluorescent illumination than under the same amount of light from incandescent filament bulbs." None of the three ranges of ultraviolet radiation emitted by fluorescent lamps has been proven to be harmful. There is no proof that it is detrimental for dark adaptation.

A new international vocabulatory [28] on lighting terms, by the Commission Internationale de l' Eclairage (C. I. E.), is now ready for distribution through the United States National Committee of the organization. Printed in three languages—French, English, and German—the vocabulary was created for the purpose of facilitating communication between scientists the world over who are working in the field of illumination. It contains 530 terms with definitions, as well as numerous symbols and formulas. Its principal sections cover radiation, photometry, colorimetry, eye and vision, lamps, light signals, etc.

Although I had not planned to cover the literature published in magazines of illumination engineering societies, this year I have to make several exceptions. First, I want to mention the Illuminating Engineering Society National Technical Conference held in Toronto, Aug. 19, 1958, where Dr. H. Richard Blackwell, formerly Director of Vision Research Laboratories at the University of Michigan, presented a new basis for establishing required footcandle levels of illumination. Dr. Blackwell, who "has been studying basic parameters of visibility for military use since early in World War II," worked under contract with the I. E. Research Institute for some eight years to develop the system which has been adopted. C. L. Crouch,[29] Technical Director of the Society, wrote an outline of this material

for the journal of the Society. This outline, together with "Report No. 1 of the Illuminating Engineering Society Committee on Recommendations of Quality and Quantity of Illumination and New Footcandle Tables,"[30] is the last word on illumination. We learn that one needs only 0.60 ft-c. illumination to read 12-point type but more than 10,000 ft-c. to see a "brown spot on a tan necktie." (Reprints of these papers are available from the Publication Office, Illuminating Engineering Society, 1860 Broadway, New York.)

Lebensohn[31] discusses the relations between vision and traffic safety in a paper worth reading but not amenable to abstracting. Some random facts from the wealth of information: The average stopping distance for a car at 60 mph is about 200 ft.; the average traffic sign can be read at 225 ft. if visual acuity is 20/20; many drivers with only 25/200 vision have had no accident in 20 years of driving; field defects are rarely the cause of accidents; the color-deficient are less confused by the red and green lights than by the red and amber; one-eyed persons or those with incipient cataract should avoid night driving; the most rapid recovery from glare occurs when yellow light is the glare source (in France yellow light for automobile headlights is compulsory); pedestrians should face the traffic at night and wear something white; glasses manufactured by The Night Driving Lens Co., of New Haven, Conn., reflect headlight glare permitting clear vision; to obtain clear night vision a −0.50 D. lens should be added to the regular distance prescription; a more reflecting road surface gives a greater distance of road visibility; of all night traffic accidents, 35% are traceable to inadequate lighting. "Accidents preventable by good light cost the nation annually 10,000 lives and $187,000.00. Modernized light is expensive but can be had at half this dollar loss."

Dr. Richards,[32] research supervisor at American Optical Co., published a fine paper on "Night Driving Seeing Problems." As he correctly states, "Driving is largely a reaction to visually obtained information. . . . Humans driving at night are working at a task for which they are poorly equipped." Some other random quotations are, "The eye uses low photopic and upper mesopic vision at civilian night driving levels." "Since low adaptation levels are not involved, tests for motorists need only measure the first ten minutes of dark adaptation." "Seeing is limited by speed." "A sharp retinal image is perceived quicker. . . . A properly placed quarter diopter cylinder has been reported to improve night acuity by 25%." "Eyes looking into a monotonous field devoid of fixation tend to . . . empty field myopia." "Another problem is aniseikonia. . . . With good lighting and familiar objects these distortions are less important, but . . . freedom from known clues brings them out." It is impossible to do justice in an abstract to this paper. It is recommended reading.

Experiments by Schweitzer and Bouman[33] reveal that against some constant background of luminance, it is only the energy content of a light flash which determines whether a pupillary reflex takes place or not. Increase of area permits the reciprocal decrease in the brightness of the flash on the condition that it remains perceptible. Increase of background brightness or background area increases the pupillary reaction threshold proportionally. It is therefore actually the relation of the flash energy to the energy which manifests itself in the luminance of the background that determines whether a contraction of the pupil takes place or not.

In a short and very fine essay,[34] Professor Schubert, of Vienna, analyzes the relationship between data offered by the modern methods of objective retinal neurophysiology (what Granit called "retinology") and the perceptual data (call it "psychophysics") of the classic period of investigation. He does this on the example of the simultaneous contrast. Such papers are important. Many of our younger researchers, totally im-

mersed in data offered by oscilloscopes, forget that their results are of significance only as far as they help to understand what is the *raison d'être* of the eye, not psychophysics but "vision." Such a paper will hardly lend itself to abstraction. Some interesting items should be mentioned, however. Schubert found that simultaneous contrast is purely a daylight-vision affair. He refers to the now famous experiments on image stabilization to make it clear that ocular movements are a necessary prerequisite for the psychophysical emergence of a contour which, in turn, is the prerequisite of contrast. He quotes Svaetichin's work on maintained discharges. This work, he feels, might, in the future, possibly throw some light upon such so far mysterious phenomena as the perception of black and what Hering called the *Eigengrau* (the visual sensation one experiences when there is no retinal stimulation).

In connection with this paper, I should mention another German study, by Grüsser and Grüntzner,[35] in which a similar paralleling of neurophysiologic and perceptual data is attempted. The twin subjects of this study are the reactions of the retinal receptors, retinal neurons, and of the visual cortex of the cat to light flashes of short duration, on the one side and the phases of the subjective after-image in man after short photic stimulation, on the other. Analysis of intracellular receptor potentials and of the intraretinal ERG shows only one hyperpolarization potential and no late reactions to coincide in time with either the Purkinje or the Hess after-image. Analysis of the neural and cortical potentials, on the other hand, makes it possible to assign the primary image and some of the phasic variations of the after-image to the activity phases of the retinal on-neurons and of the cortical B-neurons, while the dark intervals can be assigned to the activity phases of the retinal off-neurons and to the cortical D-neurons. The authors make no definite statement about the neurophysiologic basis of the first positive Hering after-image and about the role of the on-off-neurons. (Reading of this type summarizing analysis is highly stimulating. How much of the actual attributions will turn out to be correct, one cannot yet tell.)

Peckman and Hart[36] give an excellent short review of the literature of CFF (critical flicker frequency), especially an analysis of the different techniques. CFF cannot actually be expressed by some number which separates flicker from fusion. It must be approached in a statistical manner. They developed an instrument which "will conform to the requirements for statistical control." They also prefer the statistical method in the treatment of data, though a simple total score is "applicable [and probably sufficient] to clinical interpretation." "Electroretinographic estimates of the critical frequency are subject to the same laws of probability that govern the psychophysical estimates of its value. It does not suffice to record the disappearance of an amplified retinal or corneal electric potential unless that potential is correlated with the subjective response. . . ."

Simonson[37] studied the effect of contralateral glare of the CFF. The results are interesting and the discussion and interpretation extremely significant. Simonson found that CFF in one eye drops significantly when the other eye is at the time of determination exposed to a glare source. The effect was maximal at 350 ft-c., less with lower or higher intensities. The author weighs the possibility of centrifugal influences upon the contralateral eye but finds them highly improbable. He believes his results to be a proof for intracentral effect relations, the outcome of central inhibition by glare upon the time parameter of ocular excitability of which CFF is one indicator. The author cites the work of a Russian scientist, A. A. Ukhtomski, and says: "In a state of increased excitability of a motor center, additional afferent stimuli tend to produce inhibition, and the higher the state of excitability the lower is the threshold of the additional stimulus for in-

hibitory effects. In contrast, at a low excitatory state, additional afferent stimuli tend to produce a stimulation. The demonstration of a similar phenomenon in a visual function suggests that a more general physiological principle may be involved."

Mahneke [38,39] continued his valuable experiments on the flicker fusion phenomenon. With only two consecutive flashes and varying the dark interval between them, he found out that as duration of the light flashes was increased the dark interval could be decreased and still seen. (In other words, the two flashes were still seen separately.) The most marked decrease of the noticeable dark interval occurred when flashes were of 1 to 50 msec. duration. This noticeable dark interval also decreased, generally, when the two flashes were not of equal duration. In another set of experiments the number of flashes was gradually increased. Mahneke found that the necessary dark interval to prevent fusion could be decreased by 90% as the number of flashes increased from 2 to 11. With short (1 msec.) flashes, a maximum reduction is reached at about this point, while with longer flashes, there is a further reduction. At any given number of flashes, increase of their duration will decrease the length of the *noticeable dark intervals*. The number of observable cycles is the largest for a given total duration when the light-to-dark ratio is equal to 1.

Fuster [40] reports on experiments on rhesus monkeys. These had electrodes implanted into their mesencephalon; thus, it was possible to stimulate the hypothetical reticular activating system of their brain. These same monkeys had previously been trained to make visual choices under tachistoscopic presentation. The results indicate that stimulation of the mesencephalic activating system increased the effectiveness of these animals: The percentage of their correct responses increased and their mean reaction time decreased when an electric current into this system alerted them.

Breinin [41] continued his outstanding work on the electromyography of extraocular muscles. His observations suggest that "the extraocular muscles behave in a manner entirely consonant with classical Sherringtonian physiology. . . . The extraocular muscles, their nerves, and their nuclei obey the principles of spinal reflex arcs. . . . The greatest functional modification of the extraocular muscles lies in the additional feedback control mechanism of vision."

Heck and Zetterström [42] took electroencephalographic recordings from the occipital visual cortex in 100 subjects. Both on- and off-responses could be traced. Flicker fusion frequency (FFF) could be recorded objectively. (This did not coincide with subjective flicker fusion numerically.) The amplitude of the discharge tracing was greatest when the stimulus frequency was 9 to 11 per second, since in this case the positive on- and off-effects summated and the negative phases coincided. (A word about the technique will be of interest: The authors superimposed several records on a stationary film rather than obtained consecutive records on a moving film. This makes a quasi statistical average visible at a glance—a valuable improvement.) In infants up to 6 months of age no potentials could be demonstrated by this method.

I have, for years, followed (and with considerable interest) the studies of Kluyskens and his associates on the electroencephalographic measurements of the visual field. The phenomenon he calls *reaction d'arrêt* makes it possible to determine the objective limits of the visual field. In normal subjects and in those with organic brain lesions, the objective and subjective visual fields correspond remarkably. In a recent publication, Kluyskens, Titeca, and Popowycz [43] reported about 53 cases of "functional" contraction of the visual field. In these cases the phenomenon (the stoppage of the α-waves in the electroencephalogram) occurred at the usual normal isopters, while the test objects of ordinary perimetry were seen only much closer to the fixation point. (These results suggest that many of the

so-called "functional" contractions of the visual field are actually results of simulation.)

III. Electroretinography

The interest in electroretinography increases by leaps and bounds. As must have become evident by a perusal of the titles collected in the introductory section of the present Review, more than half of all papers presented in meetings of ophthalmic researchers dealt with the subject, and one of the symposia at the International Congress at Brussels was devoted to it. The electroretinogram (ERG) is also fast becoming a tool of clinical differential diagnostic investigation. Fittingly, the creator of clinical electroretinography, Prof. G. Karpe, was the guest of honor at this year's meeting (1958) of the Section of Ophthalmology of the American Medical Association. (To this, reference was also made in the introductory section.) This section will best start with a reference to Karpe's [44] presentation. Like all addresses of this type, this is meant to be read; it cannot be abstracted.

Karpe [45] and his associates continued their classic series of studies on the "Clinical Electroretinogram." In the present paper (the eighth of the series) they report about the ERG in diabetic retinopathy. The relatively low *b*-potential in many of their records corresponded with the extent and severity of the retinal damage. The ERG showed, in general, the signs which they found typical of venous stasis, a fact which further substantiates the assumption that diabetic retinopathy is intimately connected with venous disease. If there is cataract present, the ERG may give valuable information about the status of the retina.

The usefulness of electroretinography is further demonstrated in a paper by Karpe and Zetterström.[46] These authors studied four children with greatly reduced visual acuity and no definite objective pathologic findings in the eye, visual paths, and visual centers. They named the condition "congenital retinal dysfunction" and found abnormal retardation of the development of the *b*-wave in all four cases. There was no family history of eye diseases, and no consanguinity was demonstrable. Two of the children were mentally retarded; one had polycystic kidneys and died of uremia. In all, greatly impaired vision was noted at an early age.

In his guest-speaker's address (1957) before the Section of Ophthalmology of the American Medical Association, Professor François [47] spoke about the differential diagnosis of tapetoretinal degenerations. This address is mentioned here because it shows the usefulness of the methods of functional ocular examination (visual acuity measurements, determination of photopic and scotopic visual fields, color vision tests, electroretinography, electro-oculography, occipital testing of electric reactions to light stimulation, etc.) in the analysis of clinical problems.

In one of their many contributions to the clinical study of oculoelectric phenomena, François and De Rouck [48] summarized their experience in the cases of tapetoretinal degenerations. They apply the phrase "electric syndrome" to changes found (1) in the ERG, (2) in the occipital electric response to ocular illumination, and (3) in the EEG. In the group they label as peripheral tapetoretinal degenerations (retinitis pigmentosa, retinitis punctata albescens, choroideremia) the retinal response is absent or reduced; the occipital response, missing or slow, the EEG shows "diffuse perturbation." The EEG is also disturbed in Stargardt's disease and in central retinitis pigmentosa. It is normal in senile macular degeneration; here only the retinal response is perturbed. (The authors use neon and xenon strobe-light, besides the stimulus originally described by Karpe and, especially with xenon-light, often find a response where the original technique indicates extinction. They give many interesting case and family histories. The number of cases at their disposal of many of these relatively rare conditions is amazing.)

Describing a case of essential hemeralopia, François and Verriest [49] have produced a really exemplary paper. The paper shows clinical visual physiology coming of age and also shows how cases can be worked up and intelligently evaluated in an institution in which there is an opticophysiologic laboratory with proper instruments and sufficient personnel. The tests included studies of photopic and mesopic visual acuity; photopic and scotopic visual fields; dark-adaptation; color vision; electric retino-, oculo-, and encephalography, and vitamin A and carotenoid studies.

Bessière, Chabot, Dutertre, and Mirande [50,51] find electroretinography a highly practical clinical method which helps in the differential diagnosis between such cases as amblyopia and opticatrophy or retrobulbar neuritis and senile macular degeneration. It also helps to differentiate the several forms of tapetoretinal degeneration.

A paper by Orma and Vannas [52] is mentioned just to show that in the Scandinavian countries, too, electroretinography has become a regular clinic tool. In this paper, the usefulness of some drugs (of PH 203, a combination of the local anesthetic, Panthesine and Hydergine, and also of Hydergine itself) in the treatment of vascular retinopathies is discussed and ERG's studied as a means of information on their effectivity. (A discussion of the results is, of course, outside the boundaries of this review. The ERG's were not encouraging.)

Sundmark [53] studied the ERG's of a large number of patients with malignant intraocular tumor. It was found normal in cases of tumor of the iris, subnormal in cases of tumor located in the posterior region of the eye, obviously, due to the destruction of functioning retinal tissue. In a few cases of verified tumor the ERG was normal, and it was abnormal in some which turned out not to be tumors. Interesting then as these findings might be, the author correctly notes that a study of the ERG has no diagnostic value when there is a suspicion of intraocular tumor.

Another paper by the same author [54] deals with some refinements of technique. Sundmark found, with use of a contact glass electrode on human eyes, that the position of the electrode influences the size of the *b*-potential. Optimum potentials are recorded when the contact glass is placed corneally.

Several authors reported in former years that the ERG is a prognostic aid in cases of retinal detachment. Jacobson and associates [55] confirmed the validity of these observations. In 50 cases they found that the preoperative amplitude of the *b*-wave bears a direct relationship to the postoperative visual result. In no instance where the ERG was "extinguished" was a visual acuity of better than 20/200 attained, even if the retina became reattached. The ERG is, thus, a measure of retinal viability.

In the year 1956, two papers were published (one by Verrey, the other by Goar and Fletcher) about degenerative pigmentary changes in the retina of patients treated with a tranquilizer. This drug (designated as NP 207 by its producers) was supposed to reduce the undesirable side-effects of chlorpromazine hydrochloride, but in view of these effects it was never released for general use. Burian and Fletcher [56] had the opportunity to analyze two of the patients of Goar and Fletcher who suffered loss of vision through the application of this drug, with perimetric, adaptometric, and electroretinographic methods and showed that the patients have indeed suffered severe damage to both the rod and the cone systems: Dark-adaptation was delayed; the final thresholds, high, but, in contradistinction to pigmentary degeneration proper, the ERG's were not extinguished; they were only seriously altered.

Krakau [57] submitted the ERG to a mathematical treatment, the significance of which will be understood only by few. He bases his study upon a theorem developed by Helmholtz and applied by Lorente de Nó to the study of the potential field of peripheral nerve action. The experiments were carried

out on the rabbit, and directed stimuli were applied. Potentials were determined on the surface of the eye in air and in saline solution, also inside the eye, and within the retrobulbar tissue. "The character of the field is consistent with the hypothesis that a double layer is present in the wall of the eye."

Krakau, Enokson, and Hedbys [58] studied the ERG from a new and truly fascinating angle. They considered the conventional ERG tracing as a record of potential difference against time. The information is, thus, reduced to one dimension. If two electrodes are placed on the cornea (besides, of course, using the indifferent electrode) and the data fed into a two-channel oscilloscope, one can get a two-dimensional vector representation of two simultaneous ERG's. If the retina is injured asymmetrically (as was done in the authors' experiments on rabbits or as might happen by vascular lesion), the vectorial representation changes in a characteristic manner. The authors expect that localized pathologic changes in the wall of the eyeball will reflect themselves in rotations of the ERG vector.

Mitarai and Sugita [59] studied the effect of ATP and of mono-iodo-acetylic acid (MIAA) upon cone action potentials in the carp. They used Svaetichin's microelectrode technique and recorded what the latter author regards as the *L*-response to illumination. They found that ATP inhibits the on-response, activates the off-response (the recovery mechanism), and increases brightness sensitivity. MIAA decreased the amplitude of the potential, causing what seemed to be irreversible damage even in a 1/1,000 mol dilution.

Nakajima [60] found that a lethal dose of sodium malonate changes the shape of the *b*-wave in rabbits. So does a combination of sodium fluoride and sodium cyanide. The latter poisons and several other respiratory inhibitors also influence the height of the wave. Inhibitors of glycolysis have no definite influence on the ERG.

Nakajima [61] also studied the role of other retinotoxic substances, among them that of different primary para-diamino-diphenoxy-alkanes upon the rabbit ERG. These compounds caused drastic changes which disappeared in a few days. The pattern of these changes was different from that of sodium iodoacetate.

Several strains of mice have been described in the last 35 years in which total or subtotal absence of the retinal sensory epithelium is inherited in a recessive autosomal manner. François, Verriest, Rabaey, and De Rouck [62] studied some members of such a strain and found total absence of an ERG.

Elenius and Heck [63] studied dark-adaptation in two cases of achromatopsia. The course was charted with the help of the *b*-wave of the ERG. Three normal persons were used as controls. In the achromates dark-adaptation proceeded more rapidly than in normals. These data are in agreement with those of Rushton on the regeneration of visual purple, which the latter author found much delayed in normal persons. This delay suggests that in normal people dark-adaptation in the rods is inhibited temporarily by the cones.

Rendahl [64] continued his studies of the electronegative so-called *a*-potential under scotopic conditions in both healthy eyes and eyes with pathologic changes. The study of this potential should be of special interest in circulatory disturbances of the retina, where it seems to be considerably less affected than its positive counterpart. In normal eyes and in eyes with pathologic conditions without circulatory disturbances positive and negative potentials vary in a more parallel manner.

In the ERG of a man 46 years old, with choroideremia, von Burstin [65] found lack of both *a*- and *b*-waves, even when using very strong flash intensities.

Burian [66] questions the validity of the observations of Skeehan, Passmore, and Armington,[67] who in a case of retinitis pigmentosa in a Negro, reported "normal" ERG. Burian thinks that further evidence was needed to prove that the case was not one of secondary or pseudopigmentary de-

generation (as seen in syphilis or after a virus infection). Retinitis pigmentosa among Negroes is a rarity.

In their reply [67] to this Letter to the Editor, the above-mentioned authors agree that the ERG was, in fact, only similar to that of the normal and that it was progressively subnormal with increasing dark-adaptation.

Elenius and Zewi [68] made flicker electroretinographic studies on six cases of total color blindness. In four of them a scotopic type flicker ERG was found and FFF varied between 12 to 22 per second. (In one of the four cases, flicker stopped at 40 lux illumination, in the other three cases at 100 lux.) In two cases both photopic and scotopic potentials could be recorded, and FFF reached normal values only at very high intensities (60 per second at 750 lux in one case, 55 per second at 220 lux in the other). Apparently, these two were atypical cases with some of the cones functioning.

Anyone interested in an easily readable introduction into human electroretinography and a summary of work done will be delighted with the beautiful paper of Johnson.[69] He describes the changes in the ERG which result from alterations of the spectral composition of the stimulus, from changes in the adaptation level. He differentiates two positive waves which he calls the scotopic and photopic *b*-wave, respectively, and two negative ones, designated as photopic and scotopic *a*-wave. He eliminates the term *x*-wave of the more recent literature. Besides the initial photopic *a*- and *b*-waves, he also notes an off-effect, a *d*-wave complex, which is the "mirror reversal of the on-effect."

Ronchi [70] studied the *x*- and *b*-waves in their dependence upon the form rather than the energy content of the light-stimulus—an interesting new approach. He found that the *x*-wave is not influenced by the time distribution of the stimulus. The *b*-wave, on the other hand, was higher when the shape of the stimulus was triangular (the stimulus slowly rising and falling) rather than rectangular (suddenly increasing and decreasing in intensity). The implicit time of both waves was longer with triangular stimulation.

Hamasaki and Marg [71] recorded localized ERG's from the isolated retina of the frog. These showed typical *a*- and *b*-waves proving that an ERG might be a response to both focal and nonfocal stimuli. At the optic disc the ERG was absent or markedly reduced. Toward the periphery, there were abrupt changes in the amplitude of the *b*-wave. It reached a maximum amplitude in the inferior half of the retina.

Jacobson and associates [72] found that tracings from excised human retina after enucleation showed an electric response to light for as long as one hour. Procaine hydrochloride (Novocain) and lidocaine (Xylocaine) eliminated the response. Lysergic acid had no effect.

Jacobson and Gestring [73] saw evidence in some of their interesting experiments that there are centrifugal fibers in the optic nerve. They found that the ERG increased in amplitude after administration of barbiturates or section of the optic nerve and decreased when Metrazol or Hexamethane was administered. The effect of these drugs was eliminated if the optic nerve was cut beforehand. Electric stimulation of the reticular formation also reduced the ERG amplitude. Interesting cross perfusion experiments revealed, furthermore, the existence of some neurohumoral mechanism acting upon retinal functions.

Henkes [74] continued his efforts to differentiate the rod and cone system responses in the human ERG. He found that this was most easily done by evaluating the pattern of flicker responses. The rod system he studied with a stimulus frequency of 10 flashes per second; for the study of the cone system his standard was 43 flashes per second. However, frequencies up to 102 per second were applied at times. Cone-system responses can be recorded selectively by using red flashes on a continuous blue background or by recording the critical intensities and frequencies of the flicker-ERG.

Biersdorf [75] recorded simultaneous *x*- and *b*-waves with use of a red stimulus and

a- and *b*-waves with white test stimulation, both in moderate light-adaptation. The *a*-wave and the *x*-wave were found to adhere to the so-called Bunsen-Roscoe law (intensity×time=constant). The *b*-wave did not. It showed a tendency to decrease in height after reaching a maximum at some intermediate value of stimulus intensity.

Heck and Zetterström [76] investigated the flicker-ERG in 45 infants between the ages of 14 hours and 3½ months and found a process of maturing in the ERG in the first 2 months of life, although the retina is (with the exception of the macula) supposedly mature at birth. The fusion frequency of the flicker-ERG showed a maximum of 20 per second soon after birth; the flicker waves had the character of the scotopic response of the adult. Only the presence of a positive off-effect suggested the participation of photopic elements even at 14 hours after birth. By the end of the second month, both the amplitude of the photopic potentials and the FFF reach the same values as found in adults. The *b*-wave reached this maturity only at the end of the first year of life.

Dowling and Wald [77] studied rats deprived of vitamin A in their diet. At first the liver, then the blood, became depleted. Decrease of the rhodopsin content of the retinas was noted somewhat later, and finally destruction of opsin with disintergration of retinal structure followed. The thresholds of luminance to produce traceable ERG's increased as the rhodopsin percentage decreased. The height of the *b*-wave especially that of the negative *a*-wave declined. Some of the tracings, by the way, clearly showed that both the *a*- and the *b*-waves of the rat ERG are double-crested, indicating cone beside rod component reactions in rats (which frequently have been said to have a pure rod retina). After administration of vitamin A complete recovery from "night-blindness" could be proven by normal tracings of the ERG. Interestingly, recovery was fastest when all-*trans* vitamin A was administered, delayed when the 11-*cis* isomer was given, which is the actual precursor of the visual pigment. The authors conclude that opsin can only be maintained in the rods and cones when it is in combination with retinene. Since opsin is an important structural constituent of the visual cell, the latter deteriorates when the former is lost. (The paper ends with an attractive hypothesis: Possibly other proteins, too, need vitamin A to remain stabilized components of cells, and this circumstance might explain the structural disintegration of all kinds of cellular elements in vitamin A deficiency.)

IV. Color Vision

Once more it is necessary to make an exception and refer to publications in the *Journal of the Illuminating Engineering Society*. I want to mention two outstanding papers by two of the best known American authorities on technical color problems, read before the National Technical Conference of the Illuminating Engineering Society. D. B. Judd,[78] of the National Bureau of Standards, spoke on "Measurement of Light and Color" and D. Nickerson,[79] of the Department of Agriculture, on "Measurement and Specifications of Color Rendition Properties of Light Sources." These papers cover "the basic principles of measurement" and can be understood without a Ph.D. in mathematics. They are an excellent introduction into colorimetry.

Roelofs and Zeeman [80] continued their studies of the subjective (so-called Fechner-Benham) colors with use of different patterns and modifications of the classic Benham's top. It is impossible to review these experiments (in fact, I found it extremely hard to follow their minutiae) and only some of the interesting discussion following their description can be mentioned. The authors believe that color sensations are not the outcome of the influencing of some retinal substances or mechanisms (they expressly reject the Young-Helmholtz theory) but are rather caused by time sequences, changing rhythms of impulses reaching the

cortex, much in the manner in which Troland conceived of the mechanism of color vision. (The authors' exposition will also remind us of the work of Granit, according to whom the transmittance of a "frequency code" is the essence of retinal function.) (Apart from the theoretical elaboration, the experiments themselves are worth being studied and repeated. The Benham top is one of the tools of classic psychophysiology, and at least the teachers of elementary visual physiology should not pass over the impressive variety of interesting and attractive phenomena that can be demonstrated using Benham's old top and the new variations described in this paper.)

Newhall, Burnham, and Evans [81] made a valuable contribution by restudying one of the classic problems of visual psychophysics —the problem of color constancy. For this purpose they compared surface color samples with a colorimeter field while the samples were presented either (1) in full illumination, (2) with an obvious shadow falling across the sample and the surround, or (3) with the well-known hidden-shadow technique, in which only the luminance of the sample but not that of the surround is reduced. The observers had to make judgments about all three attributes (hue, brilliance, and saturation) and for all these attributes constancy was found good. The degree of constancy was expressed in terms of the so-called Brunswik ratio. (In this system, 1.00 is the index of "perfect" constancy, 0.00 that of no perceptual constancy. Actual values always are between these two extremes.) Obviously when appearances under Condition 2 were similar to those under Condition 1, constancy was good and the ratio high; when they approached more those of Condition 3, constancy was poor. The ratios were 0.50 for saturation, 0.76 for brightness, and 0.73 for over-all perceived color.

Several previous authors have described the existence of a special blue-sensitive pigment in the retina of vertebrates. These claims have evoked criticism by other experts. Now Crescitelli [82] has analyzed the retina of an Australian lizard of the Gecko family and is satisfied that his results definitely show the existence of such a pigment, of which he can state, by the way, that it is not identical with riboflavin.

Grigorovici and Aricescu-Savopol [83] measured luminosity and chromaticity in the mesopic range. They believe that mesopic vision should actually be divided into an upper range, where the error in the blue-green ratio measurement increases, and a lower range, where vision becomes dichromatic (in the sense of a tritanopia) and the green-blue ratio entirely uncertain. The coordinates of this lower mesopic dichromatic chromaticity agree with those of dichromatic vision of extremely reduced fields of observation. (Pilot experiments in the range of extremely high luminances suggest to the authors that here there is a similar reduction of chromatic discrimination.)

Ophthalmologists with a smattering of knowledge in colorimetry will hardly realize that "white" is a colorimetric problem, mostly of industry. In fact, the ISCC (Inter-Society Color Council) established a subcommittee in 1953 to study the problem of white. The report of this committee by its chairman, R. S. Hunter,[84] is now available. We learn, "A white surface is one which appears white when seen in its normal surroundings." Spectrophotometric curves show that the "white" of broadcloth, paper, paint, enamel, etc., is of very different spectral composition. The white of inorganic materials often leans toward yellow, that of organic materials toward blue.

The producers of colored materials, papers, plastics, ceramics, etc., feel the need for a physical instrument not dependent on visual judgment for the evaluation of colors and color differences. Such an instrument with three photodetectors with separate filters and photoelectric analyzers was built by Hunter.[85] "To be useful, such an instrument should measure colors of surfaces or scales giving approximately the spacing of the Munsell color system and should have

precision equal to, or better than, that of the eye trained to detect commercial color differences."

Fortunately, real color experts, like Hunter or Adams, pay only lip service to the "true" Munsell system. The "modified" Adams rectangular surface-color solid, also used by Hunter, carries Hering's four opposing colors in four appropriate loci at the ends of a red-green and of a yellow-blue axis, with purple thrown in on a side, just to conform with customary notations and notions. These color experts know that "purple" is not a basic color sensation on equal footing with the other four. With all our admiration due to Munsell for his great achievement, the replacement of his system by a tetrachromatic one—retaining, of course, his ideas about just noticeable steps of value and chroma—is highly desirable. It also should finally be understood that a rational and useful color system is entirely independent of Hering or Helmholtz or color mixing or trichromatic coordinates or what not. The efforts of the trichromatists to make any system of color conform with their ideas are pointless.

Of course, any spectrum color can be matched by using three properly chosen spectrum loci. But the user of the Munsell or other color book looks for a "match" in terms of hue, chroma, and value—not of wave lengths. Those hues are either "pure," and in this case the choice is one of Hering's four hues—red, yellow, green, and blue—or "not pure." In the latter case, the mixed hue is, in the user's subjective estimation, a mixture of any one hue with either of two of the other three hues, but never with the third, with Hering's opposing color. A red can be bluish or yellowish but never greenish; a yellow can be reddish or greenish but never bluish, etc.

The unsophisticated user of the Munsell system does not have to know anything about the peculiar place of yellow in the trichromatic theory or of its nonexistence among the CIE coordinates. The Munsell book is just as good without chromaticity diagrams, and all those forced imbrications of Munsell's system into the straight-jacket of a chromaticity diagram confuse the unsophisticated user. As for "chroma" or "value," they are for the user nothing but additions of white or gray or black to the pure or the mixed hue in quantities that are variable independently of the color. For the unsophisticated user of the Munsell or any color system, "white" is an added color, a "hueless" color which freely mixes with any hue just as Hering once described it. The user of the Munsell book need not know anything about the "composite" nature of white. In short, the user of the Munsell or any other color system acts *as if* the Hering theory were true. For him it is true, simple, and uncomplicated, in spite of all the trichromatists efforts. Using Hering's ideas, I can explain the essence of color vision to a child, but why make things simple when they can be made complicated?

As colorimetric studies are getting more refined, it can almost be expected that there will be more and more faults found with older methods and standards. Hisdal,[86] for instance, examining the spectral emissivity of tungsten, found that the relative distribution of radiant energy from a tungsten ribbon filament used as Standard Source A deviates from the energy distribution calibrated and adopted by the CIE. A lamp with a coiled filament approximates the data much better. Its use should therefore be specified for colorimetry, or the tabulated values should be recalculated.

It is with an eye for these constantly increasing demands for accuracy that colorimetrists try to reevaluate Munsell's system of color classification. Munsell was neither a physicist nor a mathematician (he was a painter), and the just noticeable steps in his color space of value or of chroma with constant hue were mostly gained by subjective comparison. One can expect that these will always be subject to relocation. MacAdam's system is newer; it has a much more rigorous intrinsic structure and "agrees better with visual estimates." Mathematician-colorimetrists will always have a hard time reconciling these two "spaces." There have

been several other attempts at improvement. The Optical Society of America has designated a Uniform Color Scales Committee for the purpose of investigating color space and providing a model which will be more nearly perfect than those now employed. A paper by Davidson and Hemmendinger [87] is a contribution toward this goal. It offers a set of comparisons at the level of Munsell's Value 6. Taking MacAdam's data as their standard for a color difference of 1 chroma-step, they have in fact found considerable discrepancies not only in the Munsell steps of chroma (most marked in the purple-blue region) but also in the directions of the constant hue lines (especially in the regions of green and red).

Breneman [88] made heterochromatic brightness matches between a variety of colors and approximate standard daylight. Chromatic adaptation to white, red, green, or blue was provided by his colorimeter. After adaptation to white, reds and blues needed less luminance to equal the brightness of the standard; greens and yellows were not similarly affected. After adaptation to red, the luminance of all test colors needed increasing to match the standard brightness. These experiments offer further evidence (if such is needed) that luminance is not uniquely related to brightness, and they also offer further evidence (if such is needed) that heterochromatic brightnesses are nonadditive. The belief that they are (which is an essential tenet of the trichromatic theory) certainly is in need of revision (as is the whole trichromatic theory).

Studies by Monjé [89] on color-normal persons showed that chromatic adaptation to red, green, yellow, or blue does not change the absolute light-sensitivity of the retina. The same was found to be true in persons with a deutan defect. Only in people with a protan anomaly does one find change of retinal sensitivity—possibly for yellow but definitely for red. The latter decreases both in the periphery and the center of the retina. Neither protan nor deutan observers showed any decrease of sensitivity for blue. (It is generally assumed that they do.) There was no change in the curve of adaptation of the protan observers. Monjé feels that these results make it possible to separate protan from deutan dichromates on the basis of sensitivity curves alone. He believes that in the first group there is a defect in the "white" substance (he obviously speaks of the so-called white-black substance assumed to exist by Hering or the dominator mechanism of Granit). In the latter, there is none. This white substance is "independent from the color sense, and is not identical with visual purple."

Some years ago (1945) Fry formulated a tetrachromatic theory of color vision in which independent red-green and blue-yellow mechanisms were assumed to subserve chromaticness, each of these mechanisms involving two photochemical substances. One of the essential differences between this theory and the classic tetrachromatic (Hering) theory relates, as it seems to me, to the locus of the response curves in the visible spectrum. In the Hering theory these curves are assumed to be juxtaposed (since the same wave length could not be assumed to anabolize and catabolize the same photochemical substance), while in the Fry theory there is considerable overlap between what we might call the red and green modulators on the one side, the blue and yellow modulators on the other. In a new paper, Fry,[90] adds some further details. He seemingly believes, like Hering, that the pigments on which the brightness of the visual response depends are not necessarily the same pigments (even the same kind of pigment) as those pigments which control chromaticness. He believes that there is a gradual transition between protanomaly and protanopia, also between deuteranomaly and deuteranopia. Fry also finds that his R, G, B and Y processes can be defined in terms of X, Y, and Z of the CIE observer. (It is indeed high time that common ground be established for the data of the physicists, on the one hand, and for the irrefutable evidence of our sensorium, the reactions of which are in terms of four—whatever the color equations will say.)

In a paper by Lowry and DePalma [91] one finds a welcome set of definitions correlating the subjective with the objective characteristics of color (e. g., chromaticness = hue + saturation with chromaticity = dominant wavelengths + purity, brightness with luminance). No quantitative relation was, however, so far established between chromaticity and luminance which the authors believe would be advantageous. In experiments designed to establish this relationship, the authors produced veiling glare which decreases contrast sensitivity. They believe that when the difference between the chromaticness and the brightness of a color sensation is eliminated it is justifiable to speak of an equivalence of chromaticity and luminance. (I find the experiments very interesting, but the significance of the establishment of this relationship is not clear to me.)

Kuwabara,[92] with use of a Japanese anomaloscope, studied the saturation discrimination of color normals and color-deficient persons. He found that in normal observers discrimination is poorest around 510 mμ and better in the blue than in the red region. Color-blind observers reveal poor saturation discrimination at their neutral point, besides. Color-anomalous observers seem to be situated between the normal and color-blind as far as saturation discrimination is concerned.

Readers of this journal should be especially interested in the background of a paper by De Kleine.[93] This author is a plastic surgeon who, in connection with some problems of skin color, became interested in colorimetry and learned about the unending and never yet successful efforts of the color experts to find suitable formulas to match their tristimulus values with perceptibility of color difference. He seemingly studied all their different systems and, since none seemed adequate to him, he now adds a hypothesis of his own to correlate "physiological response of the human retina" to "radiant flux incident per unit area." His formulas are, for me, the most easily understandable; also they make it unnecessary to enter into the lofty realm of non-Euclidian geometry to explain the perceptual color solid. (I wonder, however, if the beautiful Ostwald system would not have served Dr. De Kleine's skin-color matching problems in a much simpler manner.)

While De Kleine's equations contain only a modest square root, another system by Glasser, McKinney, Reilly, and Schnelle [94] is built on cube-root color coordinates. Color spacings derived from these equations agree with the Munsell spacing for reflectances greater than 0.5%. The system is based on Adams' well-known equations (and, like the latter, introduces tetrachromatic heresy into trichromatic orthodoxy which, even if only *sub rosa*, is all to the good).

DeKerf [95] finds only one method among the several weighted ordinate methods which determines those tristimulus specifications with an uncertainty smaller than ½ jps (just perceptible step). This is the method in which specifications are determined for every 5 mμ in the range from 380 to 780 mμ.

One Hermann Goldenberg achieved immortality of sorts by being the famous case of uniocular color blindness described by the Elder A. von Hippel in 1880. The nature of his defect is still a matter of controversy. We now have a young woman who might achieve similar immortality. She is a normal trichromate with one eye. The other eye is deuteranopic (or very close to being so). Publication of data on her case has been eagerly awaited by many of us who heard about her and about the manifold studies to which she had been subjected by a group of researchers around Graham and Hsia, at the Department of Psychology of Columbia University, in the past few years. Several of these reports [96-98] finally appeared in 1958. One of them deals with the comparison of her threshold sensitivity curves. These curves reveal that the absolute sensitivity values for blue and green (not for red) are reduced in the color-blind eye. The reduction of sensitivity is similar to that found by Hecht and Hsia (1947) and by Hsia and Graham (1957) in deuteranopia. Another report deals with hue

discrimination and color mixture data, a third one with CFF of the two eyes in various spectral regions. These data show a consistent reduction of the CFF values in the color-blind eye for all colors, including white, except for red. The displacement is constant over the luminous range, and the two curves do not reach the same maximum. In a further paper, binocular brightness matches at a photopic luminance level are reported. It was found that the deuteranopic eye required more luminance for the match in all but the red region of the spectrum. (Of course, this woman too reports that she sees yellow and blue with her deuteranopic eye—and she surely knows what she is talking about. Believers in Hering's color theory could not expect her to report otherwise, while adherents of the trichromatic theory were forced to invent new hypotheses to explain away this long-known fact.)

The classic comedy of errors represented by developments in the trichomatic theory continues to be lightly entertaining with newer and newer acts, actors, and scenery. A new and thoroughly enjoyable review of its continuing plots and counterplots is given by Walls,[99] whose knowledge of the history of this plot cannot be called less than formidable: Helmholtz, attacked by the arch-fiend Hering; rescued by Fick; rerescued by Pitt; endangered by Hecht, a friend in disguise; rescued once more by Graham and Hsia, and now the rescuers torn to critical pieces by Walls. Protanopes should see green and blue but see yellow; deuteranopes should see red and blue but also see yellow, and, heavens, those luminosity curves! According to Fick they reveal that the red-cones carry green pigment but are not missing in the protanope, and according to Hecht they are missing after all. Now Graham and Hsia almost solved the mystery, the key to which Hecht had carried to the grave, but Walls tells us that, alas, they did not solve it either. (I know of no detective story I enjoy as much.)

Belcher, Greenshields, and Wright[100] made a color vision survey on 500 subjects. They used the Ishihara, Dvorin, Boström, Boström and, Kugelberg, and AO-HRR plates and; when needed, the anomaloscope and the Farnsworth 100-hue test. Of the total, 428 passed all tests, 36 turned out to be defective, while another 36 remained unclassified, mostly owing to the difficulty of the Swedish plates. Of them, 34 could be classified as normals by retesting. Two clearly anomalous subjects penetrated into the level of color normals in all but the Ishihara test. The most interesting part of the author's study deals with the evaluation of individual plates. Some plates turned out to be nearly ideal, others very inefficient. A selection of the former from all the different sets would give a better test set than any of the individual sets.

Abnormal color perception is a frequent sequela of digitalis medication. Unger[101] considers them to be signs of intoxication. One of the author's patients complained of dazzling. Objects appeared to her "covered with snow." She had no chromatopsia, but examination with the anomaloscope and with pseudoisochromatic plates revealed disturbances of both red-green and yellow-blue vision, besides.

Verriest[102] studied the relation between visual acuity for black optotypes and background luminance in normal trichromates, color-blind and color-anomalous subjects, and subjects suffering from hemeralopia. With use of white background was higher than that of the normals in the following order: deuteranomaly, deuteranopia, protanopia, protanomaly, rod monochromatism. When background illumination was red, deuteranomalous subjects had lower threshold than normals; deuteranopes, protanomalous subjects, protanopes, and monochromates had a highly pathologic threshold. Interestingly, in green and blue light monochromates had lower thresholds than normals. For all other groups, the thresholds were higher; it was highest in deuteranopia. When illumination was low, just to permit 0.1 (20/200) visual acuity, hemeralopes had as low a threshold as normals, monochromates a definitely increased threshold. (This unexpected

result is explained by the fact that when providing low illumination, the light source had low color temperature, thus stimulating the photopic mechanism.) The higher acuity threshold in deuteranopia speaks against a simple "collapse mechanism" of red and green as an explanation for this defect. If this mechanism existed, threshold values in deuteranopia should be normal. The lower than normal threshold for green light in achromates might be explained with the "filling-in" hypothesis of Walls and Heath (1954). A similar mechanism would explain the lower threshold for the deuteranomalous in red light.

Montauffier, Riu, Camo, and Herbert,[103] in a monograph-sized paper, discuss problems of color vision from the point of view of the maritime services. Much of this is college textbook material but as such not without interest, especially for those who need an introduction. Even the expert will, however, be interested in the specific problems facing the naval medical officer in selecting personnel. Especially interesting should be the description of the two lanterns found useful in the French Navy. The authors find that neither the Ishihara test nor the Farnsworth dichotomous test are very suitable and that especially the former excludes candidates who can very well function within the requirements of naval signal interpretation. The authors point especially to the group of deuteranomalous who pass (and, in their opinion, should pass) any naval color requirement test. (It seems, by the way, that it is not only in our country that the different branches of the armed services have a hard time agreeing. The lantern constructed by Beyle, a general in the French Medical Corps, has three interchangeable sets of red, green, and yellow filters to comply with the differing filter specifications of the French Navy, Air Force, and National Railroads for the administration of the color lantern test.)

VI. Lenses, Visual Acuity, Amblyopia Low Vision

An essay by Bechtold[104] on aberrations of ophthalmic lenses will probably attract a limited circle of readers only, but those interested in more than a qualitative description of The Seven Aberrations cannot do better than to study it. The paper deals especially with the astigmatism of oblique incidence and shows how this is determined by ray-tracing formulas. Fortunately, Bechtold has done all the computation for us. The numerous diagrams and tables published with the paper give the amount of the oblique astigmatism for spheric and toric lenses of the commonly occurring powers, assuming that the obliquity of incidence is 30 degrees.

A very good nontechnical and easily understandable discussion of the principles which govern (or should govern) the manufacture of corrected-curve spectacle lenses is given by Grandperret and Roux.[105] The authors emphasize, correctly, that "ideal" correction of astigmatism of oblique incidence is not necessary, since the eye (or the mind) does not appreciate infinitesimal astigmatism. (The authors quote Professor Le Grand as the authority for a minimum value of 0.15 D. of appreciable astigmatism, to which I may add that I have had many patients able to detect 0.08 D. cylinder power added to or subtracted from their correction when looking at the Lancaster-Ragan cross dial. I agree, of course, that correction of this amount is not necessary.) Their studies resulted in the construction of a "rational" punctual (i. e., corrected curve) lens called Telor. This lens "has 'reasonably' constant power from center to periphery, leaving uncorrected an astigmatism which is below the threshold of perception." Such lenses serve their purpose better than lenses based on the Tscherning-Ostwalt principle, in which marginal astigmatism might at some peripheral point be fully corrected, while constancy of spherical power from center to periphery is, at the same time, not maintained.

Holmes and associates[106] studied the working habits of persons in all kinds of walks of life and found that different types of work or chores are performed at different distances. Ironing is done at 24 in., filing at 20. The accountant needs near

vision at 16 in. Vocational and social activities usually demand different pairs of eyeglasses, so often do hobbies and different in- and out-of-door avocations. One pair of glasses will not do. The outcome of the author's work is a richly illustrated large volume which (though it frankly aims at sales promotion) carries much useful information for those who want to serve their patients better.

Mr. Marsters,[107] Vice-President of Bausch & Lomb Optical Company, writes about "Prescribing for Multiple Visual Needs." From this paper, I learn that in the United States 77,000,000 people wear spectacles, 24,000,000 have more than one pair. Mr. Marsters addresses himself to optometrists, encouraging them to advise or dispense more than one pair of glasses to a customer. (I think this is often desirable and under our present economic circumstances mostly realizable. Surely, this is one of those instances where what is good for Bausch & Lomb is good for the nation.)

Hill [108] encountered at the Norfolk Naval Shipyard, 26 employees who complained of visual disturbances with Plano safety glasses. Sixteen were found to be in need of prescription spectacles for a minor refractive error which otherwise caused no symptoms.

Schober's [109] television eyeglasses are of yellowish tint, they absorb a part of the blue end of the spectrum, and thus increase the contrast in the televised picture. Experiments and theoretical considerations show that the absorption should be no more than 25% to 35%. The same lenses are also suitable as protective and contrast-enhancing glasses for automobile trips in hazy weather. (The reasons why a yellowish lens enhances contrast are not clear. According to lighting technicians yellowish-reddish illumination, a so-called "warm" light, is the most comfortable one when light intensity is moderate. Yellowish glasses might also absorb the fluorescence produced in the television apparatus, but this would not be a valid reason for the improvement of contrast in hazy weather.)

Emmrich,[110] who has great experience in the use of acrylic anterior chamber lenses turned lately to silicate glass lenses, which he found to have many advantages over the former. They do not absorb any of the sterilizing fluids and are free from enzymatic influences, both of which are found to cause intraocular irritation.

A paper by Elmstrom [111] raises an interesting point (though probably of only limited significance). The author publishes a graph from which it is evident that light transmission through tinted glasses decreases considerably when their thickness increases. (It decreases, for instance, in one of the often-used tints from 55% to 32% when thickness is increased from 1 to 2 mm.) "With unmatched tints there exists a possibility that they will encourage suppression of the weaker eye." (Maybe they could be used to encourage fixation with the poorer eye.)

Gernet [112] treats amblyopia with partial occlusion of the better eye. The occlusion is done with polarizing glass filters. By graded turning of two filters, the amount of light entering the eye can be regulated and any desired residual vision (from ×5/4 to 5/50) provided. The better eye should see no more, and preferably a line less, than the amblyopic eye.

Esser,[113] one of Germany's best known ophthalmologist-historians and connoisseurs (whose frequent contributions one will always read with pleasure) describes a stained-glass window of the cathedral in Strasbourg (dated from about A. D. 1180). One has at first glance the definite impression that the main figure wears spectacles with bridge and temples. This impression is given by the chance fitting of pieces of colored glass in a mosaic-like fashion to represent the eyes and of the leaden rungs which connect these pieces. (Spectacles were, according to Greeff, another famous German ophthalmologist-historian, not invented before A. D. 1270 or 1280.) The paper is beautifully illustrated. Other examples of stained windows of the same period from the cathedrals of Chartres and Rheims show a similar arrangement of

pieces but nowhere is the illusion more striking than in the window from Strasbourg which depicts an emperor.

Anybody even most superficially acquainted with optics and visual physiology will by now know that the optical images of points are not actually points and of lines, not actually lines. In fact, he will know that many phenomena of vision become better understandable if one takes into account that retinal "images" are actually distributions of photic energy according to well-defined patterns. An analysis of the distribution of energy in optical images is found in two papers by Lamberts and associates [114,115] from the Eastman Kodak Company. Photomicrographs of images show good agreement with computed diagrams.

An interesting by-line to recent politico-scientific developments is presented by studies on the detection of artificial satellites. The problem of their detection by visual means is patently related to an old problem of visual physiology—the threshold for small point sources of light. Obviously background (sky) brightness plays a role. Gulledge, Koomen, Packer, and Tousey [116] simulated the conditions of satellite detection in the laboratory and found that, as expected, it is easier against a less bright background. On the other hand, detection is made more difficult by the fact that a satellite is in motion against a background of immobile stars. Another study, by Gravey, Gulledge, and Henson,[117] shows the importance of training of "moon-watchers" and the need of changing them about every half hour to keep their efficiency at peak. The decrease in vigilance after prolonged watching was, by the way, found not to be caused by fatigue, since warning signals that a satellite is bound to appear raised the watchers' efficiency immediately, in spite of "fatigue."

O'Brien [118] approached the problem of contour perception (which, to a large measure, is the basis of visual acuity) with some interesting experiments, partly new, partly similar to the classical ones conducted by Mach (1865-1866) and by Ludvigh (1953). He used white paper forms, cut out and pasted to black discs (or black forms to white discs) and rotated them to exceed critical flicker frequency, to produce true and false contours, and to study the phenomenon of contour enhancement under varying experimental conditions. He found that contrast depends on the size of the pupillary aperture and on the nature of the edges.

Depth of focus means in ophthalmology the difference between the maximum distances, expressed in diopters, of two objects from the eye which are both perceived with maximum visual acuity (von Bahr, 1952-1955). Oshima [119] studied the depth of focus of the eye, using an ingenious mirror arrangement and a much simplified visual target, which obviated many of the objections one can raise against former techniques. He found that the depth of focus decreases (1) when the diameter of the pupil gets smaller, (2) when the brightness of test object is increased, (3) when colored test objects are used. It increases with accommodation. Oshima found that the blur in the test object became noticeable when according to geometric optical calculations a blur zone of 12 seconds of arc was formed on the retina. It seems that the ability to discriminate a blur is better than the ability to discriminate two lines as separate (40 seconds of arc). Accordingly, Oshima found that the poorer the visual acuity of an observer, the greater the discrepancy between the refraction determined by the depth of focus method and the subjectively determined value. He thinks that in cases of poor vision or when scientific accuracy is needed, measurement of refraction with the depth-of-focus technique is preferable to the usual subjective method.

Ogilvie and Taylor [120] studied the visual acuity for fine wires 0.78 and 0.94 seconds of arc in diameter. Their visibility was determined in 18 different meridians, and it turned out that they were best seen when horizontal or vertical. The threshold of

visibility is about 0.5 seconds for vertical and horizontal orientations, over 1 second for oblique orientations. There is no dioptric explanation for this fact.

We are used, since Hecht's analysis (1937), to think of visual acuity as essentially a problem in brightness discrimination, thus the two visual achievements should vary under similar experimental conditions in parallel manner. This has been questioned by more recent investigators on the basis of visual acuity determinations in intermittent light. To clarify the seeming contradictions, Nachmias [121] studied brightness discrimination and visual acuity under identical conditions of intermittent illumination. He found intermittent light less efficient than steady illumination as far as visual acuity during brief exposures is concerned. With long exposures, intermittent illumination was found to be more efficient for visual acuity than for brightness discrimination. The findings necessitate a modification of Talbot's law (which postulates equal mean energy for equal brightness). The author is correct in stating that it is hard to conceive of a mechanism which would explain the behavior of visual acuity revealed by these experiments.

Ludvigh and Miller [122] tested the visual acuity during the voluntary ocular pursuit of moving test objects (the wrongly so-called dynamic visual acuity) with a rotating mirror instrument. Angular velocities of 10 to 170 degrees per second could be introduced. Visual acuity decreased markedly as angular velocity increased. The most likely cause for this deterioration is the imperfection of the pursuit movement, resulting in displacements of the image on the retina and reduction of contrast. The deterioration is not the same for subjects with identical static visual acuity. Some might be better suited than others "to perform critical visual tasks in which the object being viewed is moving."

Miller,[123] in a subsequent paper, adds some further details to this study. He found the same decrease in visual acuity whether the target was moved vertically or horizontally, even when the observer was rotated. "Dynamic" visual acuity can be improved substantially by increasing the illumination.

Examining the visual acuity of children, Jonkers [124] found some constant discrepancies between various optotypes. The difference between the results with letters and E-charts was the smallest; Landolt rings indicated progressively less visual acuity especially in the lower acuity brackets; pictures suggested a better apparent visual acuity than did letters, especially in cases where vision was good.

Walter [125] had the original idea (he actually took out a German patent on the idea) to use the clock face with hands for the clinical determination of visual acuity. (So far clock faces appeared only on picture charts for children, but there the small patients were expected to recognize the clock as such, not the time.) Such a visual acuity chart would really be international. Details are calculated on the basis of Snellen's principle (the one-minute-of-arc rule). Recognition or nonrecognition of the position of the hands will also give information on astigmatism. The clock-face chart is thus a combination of visual acuity chart and astigmatic dial.

Prince and Fry [126] found that when the Landolt ring was not clearly visible the two subjects of their experiment were more likely to guess the break as being to the right than to the left. The bias may be due to resemblance to the letter C. Astigmatism influences the visibility of the break in some direction more than in other directions—another cause for the semblance of a bias. When the break is not actually seen there is also a chance of pure guessing of 25%.

Farrell,[127] whose book, "The Story of Blindness," I reviewed two years ago, wrote a short paper on the history of the invention of the Snellen E chart. While this was written for laymen primarily, ophthalmologists not familiar with the history of eyeglasses and of visual testing might also read it with pleasure. (Some years ago,

I suggested that this great invention and its originator be honored by posterity by giving the unit of visual acuity the name "Snellen." So far no ophthalmologic society, not even the Dutch has been interested.)

Sulzman and Davis [128] compared the New York School Vision Tester, manufactured by Bausch & Lomb, with the Massachusetts Vision Test equipment. The results were about the same. They prefer the former instrument because it requires less space and no electric extension cord, eliminates the need for a changing of spectacles, and prevents veiwing by waiting students. It also eliminates the need for "walk-ups" for nurse and student.

Colasuonno [129] reports about the feasibility of vision screening in preschool children, using the experience gained in a pilot study in one county of the State of Oregon. He found that visual acuity can be determined readily and accurately on nearly all 4-year-olds. Mass visual-acuity testing of 3-year-olds is inadvisable. The cover test is applicable to most young children. It will, at least, show possible squint and select these children for referral. Krimsky's pupillary reflection test was found to be a useful adjunct.

Arner,[130] at the Loring Air Force Base in Maine, applied the Massachusetts Vision Screening Test to 1,079 children of Air Force personnel and 830 children in the school system of a neighboring community. The "civilian" children were found to include a greater number of spectacle-wearers; they seemingly represent a sample of greater genetic homogeneity. Children wearing spectacles were found to have a significantly higher failure rate. Obviously, they were not rechecked regularly enough. The over-all validity of referrals was 81% —a good number. One of the reasons for over-referrals was the vertical phoria test. Still, the author thinks that it should be retained. He recommends the use of the +1.75 D. lens for all grades.

Moran [131] reports about preschool vision screening in Louisville. Of the 2,379 children, aged 3 to 7, a total of 179 (7.5%) were referred for professional examination and 140 were actually submitted to one. Of this latter group, 50% had a refractive error, 20% another anomaly (among them 5.7% had amblyopia), 8% a congenital defect or external disease. The factor of correct referrals was, thus, very high. Moran believes that lay testing personnel must and can be used. Of all the 16,000 preschool children that should have been tested in his area, only the above number could be screened in 18 months. With the help of lay personnel, all could have been reached.

Reinecke and Cogan [132] studied visual acuity objectively (with a modified optico-kinetic apparatus), then compared their objective and subjective visual acuity scores, and found rather good correlation. When a certain value of visual acuity was determined objectively, the subject could almost always be found to have at least that good (and frequently even better) subjective visual acuity. The finding is of importance, as the procedure might become useful in the testing of hysterics, malingerers, or small children.

Visual acuity is at first poor when the eye is exposed to glare but then improves gradually in spite of continued glare exposure for about two minutes. Simonson [133] determined this "adaptation to glare," measuring the visual acuity on fine wires of decreasing thickness and found that the increase in acuity is about 20 times the initial value.

A rather controversial technique, hypnosis, was used successfully by Browning, Quinn, and Crasilneck [134] in nine children, aged 5 to 15 years, to influence suppression amblyopia. In one case, in seven hypnosis sessions visual acuity improved from 20/80−2 to 20/30; in another case, in six sessions visual acuity improved from 20/60 to about 20/40. Nonhypnotic persuasion was much less successful. (Further study will be needed before one can agree to this type of therapy.)

Isola and Stark [135] instilled drops of isotonic salt solution (or a pilocarpine solution) into the eye with inhibition of the

visual image in strabismus. They claim that the inhibition was overcome by this simple procedure in all of their 20 cases so treated. In 2 cases of 13 with anomalous correspondence, "normal retinal correspondence was obtained by this simple procedure" (so simple, in fact, that one wishes the report were true).

The treatment of amblyopia has recently received new impetus on the continent. Like all good and new trends this trend has had many fertilizing side-effects. One of these manifests itself in a refined study of visual acuity, especially of its variations when tested with simple letters or rows of letters. Visual separation acuity, the *Trennsehschärfe* of the German authors, is usually poorer in the amblyope than visual Snellen acuity, the ability to recognize a simple optotype. A paper by Pugh analyzes the two types of visual acuity and offers some theoretical suggestions to explain the underlying mechanism. Pugh [136] thinks that the visual separation acuity in the amblyope is affected by overlapping (a motor component), the acuity for single letters by oriented distortion.

The influence of pleoptics on British ophthalmologists and orthoptists is also evident from the space devoted to the subject of amblyopia in the 1958 issue of the *British Orthoptic Journal*. To avoid possible duplication of material which will most likely be reviewed in the next issue of these ARCHIVES, I shall only briefly mention these papers. Perkins gave a good resumé of the literature dealing with the mechanism of amblyopia (he favors calling it "suppression amblopia" rather than "amblyopia of arrest," and I think his argument is valid); Wybar offers an introduction to pleoptics, giving the main ideas of Bangerter and Cüppers (I cannot well agree with this term "cortical visual acuity" for the *Trennsehschärfe* of the German authors, which means "the ability to read a whole line of letters in a Snellen's test type" as opposed to "angular visual acuity" or "the ability to read one letter isolated in a Snellen's test type," since, I think, the cortex is involved in both types of visual acuity); Douthwaite and Lee give a detailed description of results with pleoptics at the Holborn Branch of Moorfields Eye Hospital, explaining in detail the use of the apparatus and the results; Downey gives an even more detailed description of the methods with numerous illustrations of the Bangerter devices. There are two further papers on the treatment of suppression in that issue. One by Pigassou and Chadourne comes from France and shows that Bangerter's teachings have there too made an impression; the other, by Adams, is the report of a successfully treated case. (The same issue also carries a Letter to the Editor of the *British Orthoptic Journal*. This letter touches upon a problem which sooner or later will be raised wherever pleoptics becomes a serious issue, namely, the hospitalization of young children for the treatment of motor anomalies. The writer, R. A. D. Crawford, is not sure there is no permanent psychologic damage caused by the separation of a child from his family.)

The *American Orthoptic Journal* also came out with an excellent volume for 1958, of which a panel discussion on "Occlusion" is one main feature. (Obviously, the problem of amblyopia occupied the mind of American orthoptists as well.) I want to mention some papers only, (those *not* dealing with ocular motor aspects): "Development of Macular Vision," by E. H. Wood; "Fixation Disparity and Oculomotor Imbalance," by K. N. Ogle; "Aniseikonia," by M. Henderson; "Some Physiologic Aspects of Fixation Disparity," by T. E. Talbot; "The Use and Abuse of Prisms," by H. H. Romain; "Method of Testing Visual Acuity in the Amblyopic Eye, by G. F. Fonda, and an additional paper, by M. P. Lister, on "Amblyopia ex Anopsia." (This paper deals only with the classic aspects of treatment, not with pleoptics.)

Oppel and Kranke [137] found that the *Kohlrausch-Knick* (as the discontinuity which separates the cone and rod sections

of the dark-adaptation curve is often called in German) occurs earlier and at higher threshold levels in amblyopic squinting eyes than in the normal eyes of the same subjects. The explanation for this phenomenon offered by the authors is interesting. They see in it the manifestation of an "internal inhibition" which locks certain synapses in the retina and decreases the effectivity of the cone apparatus. It is this decrease in effectivity of the cone apparatus which reveals itself in poorer fixation, poorer visual acuity for single letters, and lessened ability to separate the letters in a row perceptually. (This latter faculty is the so-called *Trennvermögen* about which one reads so much lately in the German orthoptic-pleoptic literature.) The phenomenon described by the authors shows that this decreased cone efficiency reveals itself also in poorer cone adaptation. Since final dark-adaptation values were found to be identical in the good and in the amblyopic eye, the authors conclude that the rod apparatus is not involved in the mechanism which produces the amblyopia.

Mackensen [138] continued his interesting work on the physiologic reactions of the amblyopic eye. He made recordings to compare the fixation time (the time between the appearance of a fixation target in the periphery of vision and the accomplished fixation) in the normal and amblyopic eye and found it increased in the latter. The difference was even greater when reaction time was measured on some nonocular sensory-motor accomplishment involving the foveas (patients had to press a button when a light went on at the point of fixation), since retinal inhibition in amblyopia is most marked in the center of the retina.

Nawratzki and Jampolsky [139] believe that they have found a marked nasal-temporal sensitivity difference in the amblyopic eyes of patients with divergent strabismus; they also found a marked difference between the sensitivity of the two eyes of these patients. This nasal-temporal difference, they feel, is the enhancement of a normal physiologic difference between the nasal and temporal retinas.

Visual aids for close work can only be chosen properly if visual acuity for near is more accurately tested than heretofore generally done. The antiquated Jaeger notation is certainly inadequate. Keeney and Duerson [140] made a new near-vision test card which permits a more accurate determination of near vision at 14 in. in the 14/14 to 14/89 range. The metric distances at which the different types can be read by the normal eye are indicated and the A. M. A. near visual efficiency percentages are also appended. The Guild of Prescription Opticians will be glad to send the chart to all physicians performing eye examinations.

Lebensohn [141] raised several of the questions that are yet to be answered in connection with more accurate testing of near vision. What is the preferable testing distance? What is the preferable target? What is the best illiterate test? How useful are transilluminated near-vision charts? How good is objective testing of visual acuity? He offers many good practical suggestions besides.

Gettes [142] described the experiences of the Low Vision Department established at Wills Eye Hospital. Over 200 patients were examined. "Expensive telescopic lenses were ordered on just two occasions." "More patients are helped with strong reading corrections than by any other device." The author is fond of the Volk Conoid lenses and believes that all other devices "will be supplanted by the Volk Conoid lenses." He uses Stimson's optical aid manual with its new circular targets and finds that "testing appears easier with these targets than with charts." He finds the manual also "valuable for those who wish to avoid mathematical calculations." (I have to take issue with the formula

$$\text{Suggested power in D.} = \frac{\text{Denominator of Snellen fraction}}{10}$$

According to this formula one needs, when visual acuity is 20/400, a reading lens of 400/10=40 D. This is not a usable formula

because it does not state *what* the patient can read with that 40 D. lens. Kestenbaum's time-honored rule suggests that the reciprocal of 20/400 is 400/20=20/1 and that therefore 20 D. are sufficient for the reading of Jaeger 5. Lebensohn's near-vision chart shows that Jaeger 5 is equivalent to 20/40, to 8 points, to newspaper print. Why then should a person with 20/400 vision bother with a 40 D. lens?)

Ellerbrock [143] discusses the optics of various magnifying devices for the improvement of subnormal vision. Like Sloan, he chooses 40 rather than 25 cm. as the standard reference distance from which "relative distance magnification" is to be measured. Correctly he points out that the best method of magnifying for the poorly sighted is the changing to larger type. This has been successfully and extensively done in sight-saving classes. The same is achieved by projection magnifiers.

An examination of Feinbloom's telescopic lenses, as reported by Pameijer,[144] reveals that the back surface of the objective lens is in fact parabolic, the magnification is $\times$ 2.2, the over-all length two-thirds of other systems, and their appearance better than those of the latter. "The microscopical glasses certainly are something new. . . . A more powerful magnification (up to 20 times) than with the systems now in use is possible." The report concludes, "It is to be regretted that Mr. Feinbloom draws a veil of mystery around his glasses and that he does not make them available through the instrument industry." (In discussing this paper, Dekking mentions the possibility of making strong reading glasses of molded plastic. "Its casting in an aspherical shape would not be difficult and certainly not justify the extremely high price of $300.00.")

The timely monograph on "Optical Aids for Low Acuity," by Stimson,[145] came out this year in a second edition. The book provides running text material for the testing of near visual acuity from 6-point to 24-point size. Its most original feature is a test of the central visual field of the visually handicapped. The targets consist of concentric circles in which the lines and spaces subtend angles from 1 to 50 minutes when the book is held at 35 cm.

Prince,[146] on whose work I reported last year with admiration, extended his endeavors to standardize reading material for persons with subnormal vision. He found that the same size type face is better visible when spacing is less grudgingly accorded. He suggests that interletter spacing should be one-half the width of the letter "o" in each type size. He mentions "Gils sans serif medium" as the ideal type size and form. (I hope Prince will continue his efforts and publish a reading test chart for the partially sighted which includes all his recommended features. With his suggestion to retain the antiquated Jaeger notation I cannot agree.)

Fonda [147] is in favor of binocular corrections for low vision, whenever possible. He states that even with binocular additions as strong as +10.0 D., binocular vision can be maintained if the near lenses are properly decentered. According to his rule of thumb, each lens or bifocal segment is to be decentered inward 1 mm. for each diopter of reading addition.

Tillett [148] is another of the authors who discourage the establishment of so-called visual aid centers, since the testing can just as well be done by any ophthalmologist in his own practice. The author describes and illustrates proper distance- and near-vision charts, trial lenses and inexpensive telescopic lenses, and simple or illuminated hand magnifiers. He points out that many patients require more than one visual aid. He finds a microscopic trial set essential for adequate visual aid testing and recommends the Volk Conoid trial set as first choice. An illuminated magnifier trial set is desirable but not essential.

An exceptionally fine paper by Courlander [149] deals with a subject on which it is hard to say anything new—the optical appliances for the partially sighted. He pays the well-deserved tribute to Jack Lederer

who was a pioneer in producing high plus reading lenses with good field properties. He explains Keeler's method of determining required magnification clearly and well. The paper, very naturally, deals only with appliances available in the United Kingdom.

From a paper by Lebensohn [150] on visual aids for children with low vision, illustrated with interesting and pertinent case histories, I wish to quote the last paragraph: "Forty years ago our educational systems had no alternative for partially seeing children but the braille schools where instruction proceeded by necessity at one-fourth the rate of normal-sighted children. The advent of the sight-saving class changed the picture and enabled such children to approximate normal progress. As the cases cited illustrate, the education of the semisighted may be aided greatly by optical devices, and their use can expand considerably the number of children adaptable to visual education. In any individual case a prognosis of the long-range value of an optical aid cannot be made entirely on the basis of visual acuity and ocular pathology since intelligence and background, perserverance, and motivation are nearly of equal importance."

VI. Refractive Errors and Their Correction; Reading Problems

The paper "Alterations in Refraction and Their Clinical Significance," by Givner and Karlin,[151] merits well to introduce this section of my Review. These authors have brought to our attention some facts known and some not so well known but surely of significance in our daily practice. Refraction is changeable after all, and not only trauma, keratoconus, central serous retinopathy, diabetes, lenticular sclerosis, or cataract surgery will change it but many other diseases and surgical manipulations, the effect of which is less well known. Among these are muscle surgery, pterygium, chalazion, iritis, possibly measles, thyroid dysfunction, scleral buckling, corneal transplantation, the Naffziger operation, and drugs like sulfonamides and acetazolamide. The authors quote extensively from the vast experience of Castroviejo, who finds that pressure bandage after corneal surgery might well influence the refractive outcome. (Maybe that is the way a contact lens might, after all, influence the development of myopia and maybe Professor Sato of Japan has something when he advocates astigmatism surgery.) (As in the case of the intraocular acrylic lens, pioneer work in this field can hardly be expected to come from American sources. The reasons are obvious.)

Although prescribing lenses for presbyopes provides some of the butter on our bread (at least some of the butter on my bread), I always thought presbyopia as a subject for research a rather dull subject. Stenius [152] wrote a monograph on "Presbyopia and Its Correction," and, though I admire the author for his efforts and diligence, he could not convince me otherwise. I read the book very carefully but could not help having the feeling that what I read I knew anyway. It must be hard to write something new and interesting on presbyopia.

Volckmar and Willomitzer [153] compared the mydriatic effectivity on 200 patients of 2% homatropine and of a new short-acting experimental drug by Roche. The mydriatic effect was comparable. However, with use of the latter drug the postcycloplegic examination could already be performed six hours later. A comparison of refractometry with the Rodenstock instrument and with cylinder retinoscopy made it apparent that the latter furnishes more accurate results. Only when there are irregularities in the retinoscopic appearance (like the scissor-phenomenon) is the refractometer preferable. Also, its use shortens the time of the examination.

Brenner [154] uses a 2 to 3 mm. wide slit which he can turn in the trial frame during the retinoscopic examination to determine the axis of the refractive astigmatism. When the direction of the slit and of the astigmatism coincide, the whole slit is filled with light. (Brenner speaks of a device

to determine the angle of "corneal" astigmatism, which is obviously not what his device actually helps in determining. He is still not free of the prejudice that "to rely on the reply of the patient, being a subjective and unreliable manner of examination, is frequently the cause of errors in prescribing glasses." To rely on the reply of the patient is more often than not the very best method to avoid errors in prescribing glasses.)

Haynes [155] deals once more with his homokonic (he means iseikonic) cross cylinder, a modification of the cross cylinder which I mentioned in the previous issue of this Review. He uses the cross cylinder in connection with several test patterns which, like the dial, can be rotated into any desirable direction. Using a cross pattern at 45 degrees to the axis of the cross cylinder one can (as the author correctly states) in fact minimize some of those minor confusing effects of the cross cylinder test which keep many a beginner from using Jackson's most valuable tool as regularly as they should.

Raubitschek's astigmatism test was one of the very few really original contributions to the technique of refraction in our generation. (The cross cylinder test was invented before the lifetime of most of us, skiascopy still earlier. The fogging method, though refined and made clinically sound in our lifetime, is an invention dating back to the beginning of scientific ophthalmology. Velonoskiascopy never became, as far as I am aware, a clinically accepted procedure.) Addicts of objective techniques never cared for it, but even those believing in the superiority of subjective tests were chary of its adoption, since it necessitated the use of computation tables or diagrams in the form first suggested by its originator. Pascal did much but seemingly not enough to popularize it and to simplify computations. In the present year, two modifications were published, one by Eskridge,[156] the other by Bannon,[157] both of them simplifying the use of this, in my opinion, superb refraction aid. Both techniques eliminate the necessity of any calculation. (Bannon's modification is probably the superior of the two.) The first paper also includes a short description of the original and the Pascal technique.

A lens for the correction of astigmatism, in many respects similar to the Stokes lens but much easier to handle, was described a few years ago by Siebeck. Under the trade name Astikorrekt it is commercially available. Raubitschek [158] finds it an excellent aid for the determination of astigmatism and gives many useful hints for its successful application. He prefers the use of a streak retinoscope during the diagnostic procedure. (For decades teachers of cylinder retinoscopy have confused their students and each other by the use of an unnecessarily complicated terminology and seemingly contradictory description of correctly observed phenomena. It is the old confusion about "axis" and "meridian," here translated into "section" and "band," "lightband" and "guideband," etc. The "direction" of the "band" is by some authors described as coincident with the direction in which during retinoscopy it seems to roll, by others in the direction at 90 degrees to the former and in which it seems to shift. Amid utter confusion our greatest teacher of clinical optics, the late Dr. Pascal, succeeded in describing phenomena and agenda of cylinder retinoscopy in uncomplicated terms. Raubitschek, in the just-discussed paper, rekindles the issue and tells us that in the course of a long correspondence, he finally convinced Pascal that that description was wrong and that in the planned review of his book Pascal wanted to change it accordingly. Lest someone in a "revised" edition of Pascal's book should indeed revise his description of cylinder retinoscopy, I want to use this occasion to restate his original, clear, simple, and easily understandable directions: To get the right axis of a plus cylinder—if it is wrong—the axis of the cylinder has to be shifted toward the "myopic" meridian, in which the "against" movement takes place. Inversely, the axis of a minus cylinder is to be shifted toward the "hyperopic" meridian, that is,

the meridian in which there is a "with" movement.)

Eastman and Guth [159] designed a new astigmatic chart. They use the conventional sunburst of lines but with the lines surrounded by a ruling of narrower lines which, at some distance, blur into a uniform gray. When the main lines are blurred by astigmatism they blend into this background rather than become blurred. (I expect that such a chart will prove of definite value as an auxiliary. Its main defect is that there is only one main line for every 45 degrees. A good dial, like the Lancaster-Regan dial, needs one line for every 10 degrees.)

Determination of the fraction of the keratometer astigmatism one should apply to the final prescription has at one time been a favorite ophthalmomathematical game. Several rules of thumb have been in vogue one time or another, and the American Optical Co. years ago published some tables to which one can refer without any further computation. Capt. Nadbath,[160] of the United States Naval Medical Corps, adds now a new method of easy computation which he calls the "Rule of Seven or Fourteen Thirds" and which gives results favorably comparable with those one gets with more complicated computations. (Of course, one wonders when anyone would have any real need for those "algebraic gymnastics" which the Captain wants us to spare when *total* astigmatism nowadays is determined by such simpler and accurate methods as retinoscopy and the dial.)

Morgan [161] reports about an interesting long-range study. An unselected group of school children was first examined in 1934 and 1935 with respect to visual functions. Some of the same group were reexamined 20 years later. The mean age of the sample at the time of the first examination was 13 years. The number of those who could be reexamined was unfortunately rather small (51 women and 44 men). The changes were not at all startling. (The paper is interesting to us not so much for its results but as an example of proper handling of a research project in refraction and for the significance the author attaches to the various tests.)

Asthenopic systems that occur while televiewing are analyzed in a paper by Schober.[162] They are not specially attributable to this activity. They are mainly caused by wrongly corrected or uncorcorrected refractive errors or phorias. Distance corrections should be worn. In rare cases an "add" of 0.5 D. might be advisable. Since the television screen occupies only a small area within the visual field, the viewer will become dark-adapted and suffer a decrease in the differential sensitivity of his eyes if no other lights are turned on. (Television screens occupy only 5 to 6 degrees of the visual field. Regular movie screens have a horizontal angular size of 30 degrees. In Cinerama and Todd-AO processes, the horizontal field subtends up to 146 degrees.) He recommends some television spectacles to improve contrast.

A case published by Schepens and Schwartz [163] of bilateral hemangioma of the choroid should be mentioned here on account of the unusual changes of refraction which took place during a 25-year period. The refraction of the right eye changed from +2.25 to +11.00 D. sph. and that of the left eye from +0.25 to +11.00 D. sph. This could be established in retrospect by tracing the prescriptions or glasses given. Good visual acuity was retained for most of these years. Sudden loss was traceable to complicating retinal detachment.

Šmejkal [164] found, in experiments on rabbits, that tenotomy of two antagonist muscles does not produce corneal astigmatism. He also found that artificial scarring of the cornea by diathermy coagulation or galvanocauterization can cause regular astigmatism by applanation of the cornea. He feels that the making of an appropriate slit-shaped scar should be able "to achieve an adjustment of regular corneal astigmatism."

Turtz and Turtz [165] describe the case of a young man who developed myopia, accommodative weakness, and lens opacities. It turned out that he had diabetes. All

the changes were reversed by prompt antidiabetic therapy.

Another case is reported, this by Cristiansson,[166] in which acetazolamide (Diamox) caused transient myopia. The drug was given to a 27-year-old pregnant woman to decrease a large edema of hands and legs. Besides myopia, the drug caused ocular hypotony (15-16/5.5) and a fine aqueous flare. The symptoms subsided readily after cessation of treatment. (The author thinks that secondary acidosis was the underlying cause, but actual tests for this were not made.)

Alfano[167] reports and tabulates seven cases with mild or abortive forms of retrolental fibroplasia, all showing myopia. Other ocular findings included esotropia, nystagmus, paresis of gaze, pallor and atrophy of the optic disc, and irregularities of the nerve heads, of the retinal blood vessels, or of pigmentation. Visual acuity varied from seeing small objects to 20/20. In two cases, one eye was blind with far-advanced retrolental fibroplasia while the other merely showed the myopia of prematurity.

Benoit[168] had the unique opportunity to study the records of 38,670 recruits of a French military district. All but 1,548 of these young men were regular recruits of the same age (about 19 years old), came from the same region of France, had the same more or less rural educational background. The rest of them (the 1,548) were deferred recruits, thus obviously, somewhat older, but otherwise of the same origin. Among the regular recruits 1,217, or 3.38%, were myopes. Of these recruits 17,076, or 46%, were farmers, and among the latter there were 327 myopes, making up 1.91% of the farmer population. Most interesting is a breakdown of the myopic population according to degree of myopia. One sees, for instance, that among 835 nonfarmer myopes, there were 705 with myopia of 4 D. or less (some 84%); among the 298 farmers the corresponding number is 214 (only about 71%). There were percentually twice as many farmers with myopia over 7 D. than nonfarmers. Among the farmers in general 6.4% were illiterate, 55% did not finish primary education, 38% did finish, and only 0.6% had a *Brevet élémentaire* diploma. For myope farmers, the respective numbers were 9.8%, 51.2%, 34.3% and 4.7%. Of all illiterate farmers, 2.9% were were myopes, of farmers with the highest education 15.4%. Obviously schooling had some influence on the development of myopia, while existing myopia (with no correction available) kept some recruits out of school and illiterate. Interesting are the results of biometric measurements. Myopes were on the average 2 in. taller than emmetropes. A difference was manifest even among farmers, who in general were some 4 in. shorter than the nonfarmers. Myopes also tended to be of asthenic build, and high myopes had lighter iris color. "The myope is not just a wearer of spectacles for an eye adapted to close work. . . . He represents a peculiar morphologic type. Myopes are taller, thinner, represent an advanced and more and more important element of a new race of long-limbed men modeled by civilization."

A lecture by Young[169] (a psychologist with great experience in visual surveying and co-author of a study on school children in Pullman, Wash.) is good reading as an introduction into the literature on the hereditary components of myopia. He emphasizes correctly that correlation found by mathematical methods cannot, in itself, prove the relationship between two factors. His studies seem to have influenced the author in the direction of believing that "the obtained (correlation) value makes it highly unlikely that static refractive error is primarily hereditarily determined." He is in favor of experiments on identical primate twins. "It is only through the use of the experimental method that this problem can be solved."

The surgical treatment of high myopia is now finally being put to the acid test of experience in our country as well. Borley and Snyder[170] report about nine cases treated with combined lamellar scleral resection and scleral reinforcement using sclera from a donor eye. They find their

results encouraging. The procedure is, in my opinion, a rational one, and clinical trials seem to be justified. Pathologic myopia is a vicious disease, and we have been standing by long enough. (Among the cases is one with a purported myopia of 44 D. having 20/200 preoperative vision and reading "J-2 at 1 inch." It is hard to believe that such high myopia could exist. Of course, at such extreme values the dioptric degree of myopia becomes almost a matter of definition and dependent on the locus of reference from which the distance to the far point is being measured. This point, of course, is of only theoretical interest, but I wish I could know how the degree of this myopia was determined.) The authors should be congratulated on their courageous work.

One is surprised, on reading the analysis by Grosvenor [171] of three pairs of identical twins, by how different several of the oculo-optical components were in each of the three pairs. The corneal curvatures were considerably different, and so were the refraction data (unless the so-called spherical equivalent values were considered). It is interesting to note that the sibling who in two of the three sets of twins had the shorter corneal radius was also more hyperopic, suggesting that not only the corneal radius but the whole eye was shorter. The data give little support to either of the two current but opposing theories about the genesis of accommodative convergence, as both hereditary and environmental factors might account for what data on the so-called AC-A ratio were collected.

Wixon [172] measured the total astigmatism and the spherical equivalent refraction of 10 pairs of identical twins, 6 pairs of fraternal twins, and 10 pairs of like-sex siblings as controls. He found for astigmatism the following respective correlation quotients: +0.93, +0.07, +0.47. (The first is markedly close to the theoretical value, +1.00 of perfect identity.) The respective quotients for refraction were +0.99, +0.67, and +0.54, indicating the decisive influence of heredity. (Of course, this is only a small sample—and in siblings somewhat blurred by the factor of unequal age—but the number of identical twins for study in any community is indeed limited.)

"Progress in Ophthalmology," the yearly volumes of which are usually eagerly awaited by ophthalmologists all over the world brings in its current volume (the eighth) a contribution of the late Dr. Kraupa,[173] of Brno, Czechoslovakia, on the genesis of myopia. This is a small monograph of 65 pages, worth reading. Kraupa did not believe that close work has any bad influence or that glasses help. Myopia is, according to him, a malformation of central origin, nervous influences upon choroid, sclera, and retina eliciting the underlying pathologic changes.

In connection with this study, I might also mention a paper by Gardiner [174] who thinks that increase in myopia is greater and commoner in children whose diet is deficient in animal protein. He made an experiment giving a group of children 10% of their caloric intake in the form of animal protein, and he thinks that deterioration was less by ½ D. per year in the treated group compared with the control group.

Miles [175] followed the rate of increase of myopia in a group of 50 young people for nearly 20 years. Most of them show a rather uniform increase in myopia, which increase slows down around the age of 17 in the majority and around 13 in some. In 10 cases of increasing myopia treated with bifocals before the age of 13, 6 "showed an immediate and sustained decrease in myopization rate. . . .This harmless treatment deserves further use and research."

A paper by Hirsch [176] concerning the refractive changes after the age of 45 will be useful to those not familiar with statistical methods. They will find some easily understandable directives for the interpretation of this type of data. In general, the data confirm findings of previous investigators. There is some increase in the number of myopes, marked especially after age 75. There is also a constant increase in the number of hyperopes, most marked be-

tween the ages of 45 and 60. The criterion of the refractive state was "the subjective test which gives the best acuity." (This being the case, I am not sure if hyperopia really increased or only became more and more manifest. For obvious reasons, the author has used no cycloplegia.) "As age increases the number of emmetropes diminishes markedly."

Hartstein [177] gives a short description of five new types of corneal contact lenses without any discussion of their pros and cons, thus adding to rather than detracting from the confusion with which contact-lens manufacturers befuddle the matter.

Sarwar [178] reported, at a Contact Lens Society meeting in Oxford, on some unusual cases fitted with contact lenses. Among these was a case with neuroparalytic keratitis fitted with a medicinal contact lens filled with hypertonic saline. In another case a Ridley implant was made in one eye after cataract extraction. "It was considered that two intraocular acrylic lenses might be a risky procedure." In several cases, contact shells were used for cosmetic purposes rather than enucleation of an eye. In a pair of contact lenses for a case with binocular aphakia, the optics were arranged in such a way as to make the patient read through the nasal lens sections. Most likely the spherical aberration was used to give added plus power for reading. He demonstrated several cases of keratoconus and finds optical touch beneficial. Sarwar uses the Dallos technique of molding. "The majority wear their lenses for 12 hours a day continuously." (In our country, it is hard to suggest anything but corneal lenses. The advertising pressure is so terrific.)

Westsmith [179] had the original idea recommending a monocular contact lens in presbyopia. He wears a corneal contact lens of +1.50 power in his nondominant, left, eye. He sees 20/20 for distance and is undisturbed by the slight blur in his left eye. He reads J1 at 18 in. and has no trouble with the ophthalmoscope, retinoscope, or slit lamp. He also recommends the monocular contact lens in monocular aphakia, anisometropia, for corneal opacities, and for subnormal vision.

Westsmith [180] sent a questionnaire to 1,230 wearers of corneal contact lenses and received a response from 613. Only 10% of these were not wearing their lenses; of the rest, 70% wore them more than eight hours a day. Men seemed to be slightly less tolerant, near-workers more than far-workers. The greater the astigmatism the less was the tolerance. Myopes of more than 5 D. were more tolerant than those with myopia of a less degree.

Watillon and Pivont [181] described a case of progressive external ophthalmoplegia with lagophthalmus and ptosis. Special contact lenses gave excellent functional and aesthetic result.

One of the most eminent contributors to the Duke-Elder birthday issue of the *American Journal of Ophthalmology*, M. Hayward Post [182] produced on some 12 printed pages a real feat: a short course in refraction in which the fundamentals of optics, unusual conditions, bifocals, aniseikonia and vertical imbalance, prisms, aphakia, and even ocular neuroses are very adequately discussed. Such papers are a godsend for the tyro and a pleasure to read for the teacher of refraction. To abstract it is impossible.

Ophthalmologists are busy people and (whether deliberately or by default) let many matters of applied visual physiology slip through their fingers—refraction, orthoptics, contact lenses, visual aids. Educational problems, reading difficulties especially, belong in the same category (though even men of the stature of Edward Jackson did not find it below their dignity to pay attention to them). Of the following several items to be covered in this Review, none, significantly, appeared in an ophthalmologic magazine. It seems that problems of vision as related to reading and education do not often stir the creative interest of our profession. Much of the material I find it my duty to read in connection with this topic is, I confess, worthless verbiage, and I am happy that it appeared in other but our

professional journals. Some familiarity with the subject is necessary if eye doctors wish better to advise parents who come to them for help. Both as a reviewer and as a father, I can warmly recommend a book, "Reading: Chaos and Cure," by Terman and Walcutt,[183] to all who want to know about the catastrophic reading problem besetting a considerable percentage of our youngsters. The book is wonderfully partisan and hits as hard at the absurdities of the "modern" methods of teaching reading as these methods really deserve.

We should all be grateful to Professor Huelsman,[184] of the School of Education of Miami University, for his review of some recent "research" on visual problems in reading. He examined several books, papers, and doctoral dissertations dealing with three different facets of this problem. According to his laudably unbiased review, the authors whose work he studied found that "outline form perception skill *is* and *is not* related to learning to read; that tachistoscopic training *does* and *does not* contribute to attaining more rapid reading rate; and that visual skills generally *are* and *are not* related to learning to read." (All those who, like myself, feel that this type of research into causes of reading inefficiency is worthless can breathe with some relief. Huelsman's review clearly shows that this type of research leads nowhere. Good readers don't excel in any kind of perceptual or other visual "skill," whatever these words mean, and tachistoscopic or other training cannot replace the teaching of phonics, the only sure-footed method to impart reading skill.)

Nadell and Hirsch [185] made a statistical study of the relationship between intelligence and the refractive state in a selected high school sample. One will hardly expect defective mentality in a group which was capable of entering high school (even with our questionable standards of education) and will, therefore, not be astounded that the authors found no correlation of any prediction value. Possibly myopes scored somewhat better than the rest. (There is considerable older literature available on the status of refraction of mentally defective children which the authors quote. This type of children show more hyperopia than a comparable group of normal children, but even here association exists rather than actual correlation. This type of studies have, in my opinion, very questionable merit.)

Another of these statisticoeducational research projects, by Steinbaum and Kurk,[186] reveals that "in comparing the Keystone visual skill tests with both reading and intelligence no significant correlations were uncovered." "When I. Q. was not considered, the 66 subjects who failed the passing vision range showed no significant tendency for being either below or above average readers." The only "significant" correlation (+0.43) was found between far-point fusion and reading achievement. (It is surely desirable to improve fusion ability either by glasses or orthoptic exercises when such improvement is needed, and in some cases this might improve the reading score.)

The unjustified generalizations, however, continue. My rather large experience in this matter permits me to say that, for instance, a child with esophoria and convergence excess and poor divergence will be greatly helped in reading by bifocals or that an occasional case with aniseikonia will, after correction, show marked progress, but it is not, in general, true, as Bing [187] contends, that "recent research tends to point to the need for good binocular functioning at the reading distance." Many children with strabismus are superb readers. Effortless binocular vision or none are needed for effortless reading. Only within such limits is it justified to state that "improvement in visual functioning facilitates reading achievement." Poor reading is an educational problem first of all, a visual problem only in the exceptional case, a neurological problem only in the mentally deficient, a psychosocial problem only secondarily, and a psychoanalytic problem probably never.

A paper by Robinson, Letton, Mozzi, and Rosenbloom [188] belongs in the negativist

group. These authors used a so-called Children's Visual Achievement Form (one of the publications which are the contribution, probably misguided, of our Lions Clubs towards "Eyesight Conservation") for the study of pupils in the first grade of school. They found that such a test is unsatisfactory to predict intelligence level or reading achievement.

One of the papers which answer the question of correlation between form vision and scholastic achievement in the positive stems from Dr. Kephart,[189] of the Department of Psychology, Purdue University. Dr. Kephart is one of those scientists for whom *all* vision, including not only form vision but the seeing of figure from ground and even contour appreciation, is a learned function. He reports about "perceptual-motor training activities integrated with class room work" in a second-grade classroom which to him "rather strongly suggests that achievement at the first grade level can be markedly affected by the addition of . . . activities designed to assist the children in the development of form perception." Some of Dr. Kephart's statements are, no doubt, correct. Surely contour has to be appreciated, figure has to be recognized from ground, form has to be recognized, I may even add that vision is necessary *before* a child can be taught to read, but poor readers can do well in perceptual skill tests and still read poorly. That the mentally retarded child is poor in perception and predictably poor in school achievement is no doubt true, but that is a different problem. To "assist the children in the development of form perception," and I mean *normal* children, "at the first grade level," is, in my opinion, a pitiful waste of classroom time. A good course in phonics will achieve much more than all kinds of "activties integrated with [the author would have been more accurate in saying: replacing] classroom work."

"Hypothyroid cases with slow speed of visual perception should not be confused with cases of slow speed of word perception due to educational rather than endocrine causes," writes Eames.[190] "Briefly, medication cannot take the place of instruction."

Ophthalmologists will hardly be interested in teaching people how to increase their speed of reading. Seemingly some optometrists feel this falls within the limits of their obligation to the public. Two brothers Armistead, who hold degrees in education and optometry, developed the "Armistead Technique" and published a book on "Speed Reading and Visual Training" in 1955. An "Indianapolis Reading Institute" set up in a local hotel gives 13 two-hour weekly sessions to improve reading speed by a tachistoscope technique. The published data [191] for achieved improvement of speed without loss of comprehension are very remarkable.

VII. Clinically Useful Optical Procedures

The Chairman's address read by Pischel [192] at the 1958 meeting of the Section of Ophthalmology of the American Medical Association should encourage many in the routine slit-lamp examination of the eyeground. A salient and significant clinical observation should be mentioned. Discussing the differential diagnosis of intraocular tumors, Pischel states that "transscleral transillumination has proved absolutely unsatisfactory to me." Surely the slit lamp and the Goldmann three-mirror contact lens are superior diagnostic tools.

The new Zeiss biomicroscope has a Hruby lens as an accessory. The only disadvantage of this is the invariable distance between the patient's cornea and the concave lens. Hruby [193] suggests a simple rack-and-pinion arrangement, which permits variation of this distance to find the most advantageous lens position for biomicroscopy of the inner eye.

Ogg [194] attached an infrared filter and converter tube to the Zeiss slit lamp. This enabled him to photograph the eye in darkness and to examine the iris and pupil of eyes with corneal opacities. It did not make it possible, however, to see retinal detail through a cataract. A malignant melanoma

was made to stand out clearly against a transparent secondary retinal detachment.

Swanson, Rose, and Taube [195] developed an adjustable swivel type of platform which can be mounted directly to the new Zeiss slit lamp (probably to other slit lamps too) to facilitate the examination of animals.

A device invented by Friedman and Good [196] for rotating the beam in the Goldmann slit lamp will be a welcome addition for owners of this excellent instrument, as it increases its usefulness when applied to goniscopy. (By the way, the latest model of the Haag Streit slit lamp is so designed as to eliminate that only serious defect of the older model, which this ingenious new device is meant to correct.)

Broggi [197] made a welcome minor refinement on the ophthalmoscope by replacing the usually rather large aperture disc or cap with one having a much smaller (pin) hole opening (1.2 to 1.5 mm.). Reflections are diminished, and the study of the eye-ground even with undilated pupil facilitated.

Donaldson [198] constructed a binocular indirect ophthalmoscope to yield an upright stereoscopic fundus image. Such an instrument is certainly interesting, though the author does not expect that commercial production of it would be warranted.

Ross [199] had the original idea to detach the Schepens ophthalmoscope from its headband. In this manner he can use it as a hand ophthalmoscope for binocular or monocular indirect ophthalmoscopy with a powerful light source even during surgery without having to wear a heavy contraption on his head all the time.

From the fine paper by Schwartz [200] on postoperative ophthalmoscopy after retinal detachment surgery, the following sentences are worthy to be quoted: "The brighter light, larger field, and minimal distortion of the Schepens binocular indirect ophthalmoscope make it possible to study the fundus even on the first or second postoperative day. Stereopsis and great depth of focus are further advantages of the Schepens ophthalmoscope. Efficient use of binocular indirect ophthalmoscopy permits better evaluation than with any other instrument."

Havener [201] described the many advantages of the Schepens binocular indirect ophthalmoscope, of which he is an enthusiastic user. "The non-indirect ophthalmologist will stoutly and rightly mention that the indirect ophthalmoscope is a monstrosity . . ." (I never knew that we ophthalmologists can be classified into indirect and nonindirect varieties. One always learns something new. But I hope, with the author, that the latter species is due for extinction.)

Though ultrasonic reflection can only with some imagination be ordered among optic phenomena, short mention should be made of a paper by Baum and Greenwood,[202] in which details of an exciting new localizing method are described. They coined a new word, "echogram," which, I feel, will soon become a much-used medical term. The cases on which they demonstrate the advantages of their technique are complicated retinal detachments, vitreous hemorrhages, tumors, and foreign bodies.

Oksala and Lehtinen [203] were able to diagnose the rupture of the sclera with ultrasound in a case of contusion of the eyeball with persistent hypotony where the ophthalmoscopic examination failed to clarify the condition.

Weekers and Bonnet-DeRudder [204] use the binocular Zeiss surgical microscope in combination with the Goldmann gonioscopic prism for gonioscopy of patients in the reclining position (e. g., during surgery or general anesthesia and especially in children or infants).

Ziv [205] described a new contact lens for recording the ERG in rabbits.

Klein [206] constructed a self-luminous Placido disc which is convenient to handle, readily portable, and independent of external illumination. With the instrument one can examine the whole paracentral area of the cornea in a few seconds. The keratoscope head fits the Keeler Ophthalmoscope handle.

Lowenstein and Loewenfeld [207] described their new electronic instrument for the re-

cording and analysis of pupillary movements (the Electronic Pupillograph) and gave several examples of its application for clinical analysis. (A useful bibliography of previous work of the authors is added.)

Jonkers and Jongbloed,[208] from the Physiological Laboratory of the University of Utrecht, describe a new adaptometer, a synthesis of the original Jonkers and the Goldmann-Weekers instrument. With this, one can determine the increase of sensitivity in the whole visual field or parts of it, subjectively or objectively, and with white or colored lights. There are provisions to test contrast sensitivity and visual acuity with optotypes during accommodation. The instrument registers the threshhold values automatically on a logarithmic sensitivity scale. Its range extends five top units.

Stein [209] uses a commercially available triple "circline" fluorescent tube and any direct-focusing 35 mm. camera as a keratograph. Since the target is plane (like the time-honored Placido disc) and the cornea a convex mirror, there is a certain distortion of proportions to be expected. "However concentricity is unaffected and distortions manifest themselves irrespective of the target planarity."

The same author [210] redesigned the Burton unit for black-light illumination to facilitate alternation of white and black light without disturbing the mesopic state of the observer. The unit is mounted on the Burton "Fleximatic" support, which lends mobility to the unit. A binocular loup is recommended to give additional magnification.

The entopic visibility of the Purkinje (vascular) figure and of the macular shagreen gives valuable information about the functional status of the retina, especially the macular area. Ehrich gives useful hints on how to elicit the phenomenon. (He uses the concentrated strong light of the euthyscope for this purpose. Any other strong concentrated light, especially that of the Keeler ophthalmoscope, will also do.)

Berger, Mahneke, and Mortensen [212] describe an electronic flash generator for experiments in "psychophysiological optics." With this instrument they can produce simple and multiple light flashes and independently vary intensity, frequency, and light-dark ratio. They can also superimpose one flash on another.

Jacobson [213] described a precision light source for electroretinography. Duration and intensity of the stimulus flash are continuously variable with this unit, and two or more of them can be flashed alternately.

Many of us will remember the startling demonstration of unexpected detail in microscopic specimens presented in the several exhibits of Cibis, the inventor of a new illumination system. An analysis of the technique (which is too technical for abstraction) is given by Drews.[214] He rightly refers to the new phenomena as "Cibis-effect" and believes that they are the outcome of a special form of dark-field illumination.

A photomultiplier tube is used by Cornsweet [215] to record oscillations of the eye as small as 3 to 4 degrees, with an accuracy of 10 seconds of arc. He focuses a small spot of light on the optic disc of the observer which, when the eye turns, moves back and forth over it. Since blood vessels absorb more light than the whitish background, whenever the scanning spot moves over a blood vessel, a deflection is registered by the oscilloscope. Changes in this deflection represent movements of the eye. (Their extent can be very accurately calculated from the oscilloscopic record.)

McDonald and Light [216] modified a Bausch & Lomb Microprojector to be usable for photocoagulation of iris and retina. In the first case, a +35.00 D. lens is used to focus the light of an electric arc on the iris; in the second case, the lens of the eye does the focusing. So far they have used the instrument only on rabbits. (Photocoagulation is certainly an interesting and exciting new method. Its clinical evaluation is beyond the boundaries set for this review.)

Guerry, Wiesinger, and Ham [217] made their own instrument for photocoagulation

(and reported about a successfully treated case of angiomatosis retinae).

Vörösmarthy and Pénzes [218] did even better. They used sunlight concentrated by a simple strong convex lens to produce an artificial pupil in a case of aphakia where the iris was pulled upward—they made a photoiridotomy, so to speak.

Kurland, Sachs, Kerrelman, and Davis [219] took it upon themselves to evaluate a device called "Phosphenator," advertised and marketed for the "rapid diagnosis of glaucoma." I reported about this device in the previous issue of this Review and emphasized the poor and unreliable fashion in which its "creators" presented the clinical evidence for the usefulness of this instrument. The study by the above-mentioned authors on nearly 150 veterans, patients, and employees of Walter Reed Hospital proves that this device is of no value.

Lytton [220] describes two simple devices which help fixation in perimetry and campimetry. For the former he uses a cone with small aperture. When one looks through this, the fixation target appears "framed" and fixation "becomes easier and steadier." For campimetry, he uses a much larger truncated cone which the examined subject holds against the orbital margin. A wire cross with central ring is fitted into this cone. The subject looks at the fixation mark through the ring. The fixation is facilitated by the cross wires. (I think both devices are excellent.)

Hilton [221] made a nice little fixation device for one eye while the other eye is tested for unilateral central scotoma. (Since it can be "home-made" and will cost less than $1, I doubt if anyone will use it.)

Zeller [222] used paddles or sticks covered with black felt (the same material as the tangent screen) to carry multiple targets into the visual field. "The use of multiple targets will often detect early pathology missed when single targets are used." Multiple targets can also be used pinned to the screen and in this manner the brightness of the fixated and paramacular targets compared. (The method should prove a welcome addition to refined campimetric technique.)

A portable visual colorimeter constructed by Miller and Sant [223] of Eastman Kodak Company permits measurement of color and luminance either in Maxwellian or in telescopic viewing, indoors and outdoors, and even of small color samples. Matching is done foveally at the border between a small central colorimetric field and the external test field. The precision of the instrument was found satisfactory, compatible with the requirements symbolized by the well-known MacAdam "ellipses of just-discriminable color difference."

Berens [224] used red, green, blue, and white enameled balls in a wooden box to test the visual acuity and color vision of small children. The balls are 15, 10, 5, and 3 mm. in diameter and at 25 cm. subtend the approximate visual angle of 3, 2, 1, and ⅔ degrees, respectively. The size of the ball for which the child will reach gives some indication of its visual acuity. Older children can be tested for color discrimination by being asked to pick out a red or green one from an assortment of balls.

Schober [225] described a portable optometer (less than 1 lb. in weight, less than 1 ft. in length, fitting into any doctor's bag) with which refraction (between +20 and −20 D.) and accommodation can easily and relatively accurately be measured at the bedside or wherever use of regular equipment is not feasible. The testplate is illuminated by a battery flashlight. It carries a dial for the determination of astigmatism, (and) Snellen letters of decreasing magnitude.

Halberg [226] reminded us that the old De-Zengg refractor makes a flexible aid for retinoscopy providing a fairly complete battery of lenses. "It is a handy unit to have in the medical bag for clinic or bedside use."

A handy near-vision unit is suggested by Carbo.[227] This device can be attached to the reading card clip of the near-point bar of any standard refractor. It contains a muscle light and reading and color test cards. When not in use, it can be swung out of position.

Refracting a patient with marked ptosis or blepharochalasis might be difficult. Cardell [228] advised the use of a ptosis wire to lift the lid. The wire is mounted on a ring which fits into the back cell of the trial frame.

Trotter and Stromberg [229] suggested the use of a linear xenon-filled flash tube for the production of the after-images for the retinal correspondence test. The flash lasts only 1/1,000 second and therefore requires only momentary fixation. The after-image is intensive and of long duration. Many children with whom the authors were unsuccessful in eliciting an after-image with the old incandescent filament method responded easily to testing with the new technique.

Ophthalmologists will also be interested to know about an automatic electronic focusing device for ophthalmic lenses (a kind of super lensometer) developed by American Optical Company.[230] With this instrument, lens inspection and quality control are enhanced and surface aberrations can be determined. "A great deal of information about the performance of a lens can be obtained quickly and accurately."

Goodstein and Goeller [231] use a stereoscopic closeup lens manufactured by Zeiss with the Kine Exacta camera to produce stereophotograms of the anterior segment of the eye and the chamber angle. They describe their technique as rapid and simple and the equipment as relatively inexpensive.

Norton and Sullivan [232] described a practical dual-exposure technique of retinal stereophotography and gave much valuable technical information to improve retinal photographic standards. (I admire the level of technical knowledge displayed in this paper but feel that such high sounding terms as "absolute" and "relative" stereophotography—which simply mean "simultaneously recording" or "dual-exposure" techniques—should be avoided in a scientific publication.)

Cockburn [233] replaced the eye-piece of the Bausch & Lomb binocular ophthalmoscope by a single lens reflex camera (Wirgin, Edixa, 35 mm.; Cassar 1:2.8 lens) and uses the standard light source of the instrument for black and white fundus photographs. For color photography, a photographic flash lamp is added which is connected to a capacitor type flash unit. Needed exposure time is 1/25 second, diaphragm opening is 2.8 to 4.0.

Rasmussen [234] uses the biprismatic stereoattachment made by Zeiss on an Edixa-Reflex camera and 1/1,000 second electronic flash to make 16×22 mm. stereoscopic color photographs. The flash permits use of smallest diaphragms and gives depth of field. The color temperature is adapted to daylight film.

The Goldmann applanation tonometer is an instrument for the measuring of intraocular pressure and, therefore, reference to it in this Review would seem to be out of order. In fact, it is not. The instrument represents the application, in the most brilliant manner and for a purpose of great clinical significance, of an optical principle, the measurable double displacement of an image by two opposing prisms. A short description of the instrument and of the mode of its application by Moses [235] is, as far as I am aware, the first in the American ophthalmologic literature.

Binder and Skelly [236] made a device for the teaching of refraction in the lecture room. It consists of a silhouette of an eye, different inserts to demonstrate refractive errors (like astigmatism), and two dowels which represent the course of rays.

Smialowski and Vaile [237] published short but sufficiently detailed instructions for the composite mounting of 35 mm. color transparencies. (Such composites are good visual aids for teaching or lectures. They permit the showing of more than one view at the same time, using but one projector.)

VIII. Space Perception, Stereopsis, and Aniseikonia

Reference to a beautifully written philosophical essay on "Localization" by Colenbrander [238] will aptly introduce this section. It is impossible, however, to give the es-

sence of this essay in a few sentences. Here are some random observations: Aural, haptic, and optic space do not agree with each other fully. Each sense gives a distorted picture. In visual space great distances are underestimated. Slopes appear steeper from a distance. The speed of motion is underestimated at a distance. What we see above seems higher, and what we see below is flatter. The acuteness of angles is underestimated. Right angles must in paintings be represented in acute angles, and we readily interpret the latter as right ones. Examples from the studies of Helmholtz, Hillebrand, and Blumenfeld show how visually straight or parallel lines are not actually straight or parallel. "It is possible that two convictions which seem to contradict each other can be equally and simultaneously true. . . . Our reason is bound to limits which are too restricted to embrace the whole world." (All this may be so—but surely it is beyond that field of scientific endeavor which in this Review it is our duty to cover.)

Dutch ophthalmologists seem to keep up the old tradition of psychophysiologic studies of space perception, and it seems that it is not all rear-guard action of an older generation. A young lady ophthalmologist, C. M. J. Velzeboer,[239] has found the subjective localization in normals and in squinters sufficiently interesting to write a doctoral dissertation of some 160 pages on the subject. She discusses egocentral optical localization under binocular conditions, with monocular vision, and in squinters; the optic median plan in squinters, and what she calls reciprocal localization (roughly identical with retinal correspondence) in both normals and squinters. She knows her literature, and the experiments are sound. She believes that when one finds abnormal reciprocal localization, "there is a process of adaptation between the impulses evoked in the right and the left eye that reaches its fulfillment in the development of an abnormal cortical junction."

Mackworth and Mackworth,[240] of the Applied Psychology Research Unit in Cambridge, England, published what in my estimation is one of the most beautiful pieces of research in applied visual physiology in recent years. By the use of television techniques they recorded the changing directions of gaze as a person looks upon a picture or scene. (This was done by picking up the corneal reflex by a television camera.) If the scene at which the observer was looking was provided by another television camera, then the movements of the corneal reflex could be monitored upon a third television screen showing the same scene. Thus, it becomes for the first time possible for an experimenter to see where a person is actually looking when watching a moving scene (or even a still picture). As a matter of fact, one can, with still another television set-up make a permanent record of the composite scenery-and-eye motion view. The uses to which this system of recording can be put seem to me almost unimaginable. I am sure that psychologists, advertising experts, and people in show-business will soon learn a lot through this arrangement about what "catches" the eye. Of the interesting examples recorded in the paper, one is the "Fall of Icarus" by Pieter Brueghel the Elder. (Why the authors chose this of all paintings to show a scanning eye-marker should challenge a psychoanalyst.) Another is "a pilot's view when he is 180 feet above ground about 25 seconds from touchdown" —a no less exciting scene.

Mackensen[241] thinks that the slow phase of the optokinetic nystagmus is not a simple following movement. Its angular velocity is less than that of the rotating pattern. This causes a shift of contours on the retina, which, in its turn, induces a refixation movement. This is the slow phase. The fast phase is not merely a release of tension for the return to some initial zero-position. The midposition of the eyes affected by optokinetic nystagmus is shifted in the direction of the fast phase. The fast phase occurs under the influence of subcortical centers which regulate autonomous rhythmic impulses.

Ever since Poppelreuter and W. Fuchs, after World War I, published their now classic studies on the mode of vision in case of homonymous hemianopia, we have known that one of the striking features in their visual behavior is a change of directional values within their perceived visual context. Bruell,[242] in simple but very convincing experiments, showed that normal people too make a misjudgment of visual direction if in an otherwise empty visual field visual stimuli extend to one side of the fixation point only. He attributes this shift of "retinal local signs" to an asymmetric retino-occipital stimulation pattern and believes (I think correctly) that "shifts of retinal space values occurring in strabismus . . . belong to another class of phenomena." (One wishes that the antiquated concept covered by the term "retinal local sign" would fall into well-deserved oblivion. Sensed direction is determined by the context of visible patterns and their relationship to body image. The retina carries no kind of local signs.)

Perception of motion has an upper and lower speed threshold. (A point which moves slower than lower threshold speed is not seen to move at all; a point which moves faster than upper threshold speed gives the impression of a stationary streak across the field of vision.) The influence of luminance upon the upper of these two thresholds was studied by Brown.[243] The greater the speed of motion across the field of vision, the greater luminance was needed to keep the motion within the limits of being detectable, at least in the realm of moderate luminances. At high luminance intensities, the upper speed threshold rose to about 35 degrees visual angle per second, at which value it then remained constant even when luminance increased further.

A vertical string extending in front of a uniform background is seen in stereoscopic relief, a horizontal string is not. When the string is tilted from the horizontal into the vertical direction, the stereoeffect appears at some angular value (near 30 degrees) of the tilt. Verain [244] believes that this value can be used as a characteristic of stereoacuity. The test will also detect those having no normal binocular vision. (The stereoscopic effect elicited by oblique lines is, of course, the basis of Ames' space eikonometer test to which the author makes no reference.)

The new mathematical approach to problems of binocular vision by Luneburg has, after its orginator's untimely death, found a champion in his collaborator, Professor Blank. Two papers by this author [245,246] are to be mentioned in this year's Review. Reduction of empirical visual factors to the most rudimentary aspects of visual experience and their association with mathematical postulations make it possible for Blank to develop the special axiomatics of binocular vision and to build a foundation of geometry under space perception. These axioms and their development is the subject of one of the papers, the conclusion of which will by now be familiar to all acquainted with the Luneburg-Blank concepts: "Visual metric cannot be equated to the physical metric . . . . Visual straightness is not the same as physical straightness . . . . There is no evident a priori advantage to postulating a Euclidian metric." An analysis of experiments in binocular visual perception is the subject of the second paper.

Gogel, Hartman, and Harker [247] conducted experiments to determine whether the retinal subtense of a familiar object would determine its apparent absolute distance. Interestingly, the results answer in the negative. The authors found "no evidence for the presence of absolute-distance perception as a function of retinal size." However, if they *apparently* presented the same object several times successively, only changing the retinal subtense (this is easily done, for instance, with playing cards, the actual size of which can be varied), then the score of distance judgment did improve. This the authors interpret in the sense that "relative-distance perception as a function of the relative size of familiar objects can occur without the concomitant occurrence of absolute distance perception."

Experiments by Harker [248] in which both monocular and binocular depth clues were

available to the observers show that both add to binocular depth discrimination. Thus, in natural environments it is justified to refer to a composite binocular depth acuity.

Ogle [249] studied the stereoscopic threshold in an instrument which eliminated empirical factors as much as possible at two viewing distance, 0.5 and 10 meters. He found no change in stereoscopic acuity. These results are in seeming contradiction with data in the literature, according to which depth discrimination acuity increases with distance. Obviously the latter phenomenon is the outcome of purely monocular vision and is due to our ability to discriminate differences in the angular size of objects. (If experience makes us assume that two objects of unequal visual angular size are equal, the difference is interpreted as difference in depth.)

Seldom will one find anything entirely, even surprisingly, new in the field of studies on stereoscopic vision, and a reviewer is happy if he has occasion to report on something that is new. Dove's experiments (1841), in which stereograms were viewed during short illumination by an electric spark, have been quoted now for over 100 years to prove that convergence and proprioceptive influences from the extraocular muscles are unnecessary for stereopsis. Ogle and Weil [250] studied these temporal aspects of our stereoscopic acuity in greater detail and found that some qualifying statement is needed. In fact, they found that as exposure time diminishes from 1 second to 1/125 second stereoscopic acuity deteriorates rapidly. The authors make the brilliant suggestion that stereoscopic acuity, like visual acuity, might be enhanced by the constant nystagmoid excursions of the eyes. This enhancement needs time and when patterns are presented for very short durations the stereoscopic acuity mechanism is unable to become operative. One will remember that "stabilization" of the retinal image (as reported in previous issues of this Review) also tends to have a deleterious effect on vision and probably for similar reasons.

Renshaw [251] gives an interesting new interpretation of certain phenomena associated with "stereoimage decentration." He considers the well-known effects of the decentration of stereograms upon perceived object size (macropsia when decentration is uncrossed, micropsia when it is crossed) to be purely psychological. He speaks about a stereofield (a solid angle with two centers of projection in the sense of Luneburg's polar coordinates). This stereofield decreases with the increase of the distance of regard. It also decreases when the stereoimages diverge (are uncrossed). Diverging (uncrossed) stereoimages appear farther, according to the author, because of this mental association of distance with diminished stereofield. The opposite holds for crossed stereoimages viewed in overconvergence.

Binocular vision peering into instruments does not prove effective binocular vision in "free space" (commonplace surroundings). Analyzing the effective binocular vision of patients treated by orthoptic or pleoptic methods, Görtz [252] found that, for instance, all of his 49 patients with straight eyes showed normal correspondence in the synoptophore but only 36 (73%) of them under normal conditions of vision. In 21 cases with straight eyes and amblyopia in one eye, this number was reduced to 13 (62%). If there was some residual strabismus left after surgery then around 80% of them showed normal correspondence in the synoptophore but only about half of these under ordinary conditions of vision. (The functional status in "free space" was tested with a polaroid spectacle arrangement.)

A rather neglected subject, dysmegalopsia (erroneous visual discrimination of object size) is discussed in two interesting papers by Gramberg-Danielsen.[253,254] He differentiates between errors in judgment which are psychological (he mentions as causes inexperience, lack of learned size constancy, "infantilism" of perception occurring especially in Graves' disease, and hysteria) and actual dysmegalopsia based

on organic change in the receptor mechanism. Only the latter is of clinical interest to ophthalmologists. Into this group belong aniseikonia in aphakia, micropsia due to macular edema, retrobulbar tumor or chorioretinitis, macropsia due to retinal scarring (very rare), and metamorphopsia. The best known instances of dysmegalopsia are connected with disturbances of accommodation and convergence. At a certain stage of recovery after the application of atropine, there is a greater than usual accommodative effort necessary for the effectuation of a given amount of accommodation, and an error in feedback makes the object of attention appear closer and smaller. (One is pleased and interested to see concepts stemming from cybernetics more and more intruding into European, especially German, medical thinking.)

In last year's Review, I reported about the use of sterophotograms made by Cohen, Forman, and Milan of the space eikonometer for the purpose of screening aniseikonia. Milan and Waldstreicher [255] undertook a clinical evaluation of this method. Possibly some errors crept into the preparation of the slides, as the comparison with data gathered with the AO clinical space eikonometer shows a constant discrepancy. Applying a correction factor for this discrepancy the findings with these less expensive stereograms correlate well with the clinical space eikonometer data, within approximately 0.5%. The declination values approximate those obtained with the clinical instrument within 0.14 degree. "The stereo slides used in conjunction with a standard stereo viewer seem to have a definite value for use as a suitable instrument for screening aniseikonia."

Brecher, Winters, and Townsend [256] compared the size and shape of perceived uniocular images by alternating these images slowly enough to prevent binocular fusion but still fast enough to permit comparison. Aniseikonic corrections obtained by this method and with the space eikonometer method revealed no consistent correlation, and the reproductibility of results was much poorer with the former method than with the latter. The authors think that "the image retention method for aniseikonic determination may be primarily of value for those persons who have poor binocular fusion" (though one wonders why anyone would like to measure aniseikonia in this type subject, at least with any clinical benefit in mind).

The faculty of sensory fusion reaches, according to Sachsenweger,[257] different degrees of effectiveness, even in the normal. Its lower degrees approach conditions found in the patient with concomitant strabismus. These lower degrees manifest themselves in an increasing lability of fusion and in an increasing unilaterality of vision with marked ocular dominance. Even in the normal, ocular dominance influences the primary binocular visual direction and the position of the so-called cyclopean eye; in the patient with unilateral strabismus, the phenomenon of ocular dominance reaches extreme degrees. In alternating strabismus, it is the lability of fusion which reaches extreme values. Poor sensory fusion is mostly a consequence of strabismus. However, in connection with some other factors, it may also be one of its causes.

Kruger and Jahner,[258] have done a real service by examining a group of patients with bilateral aphakia for their binocular vision. It was poorer in the younger age group (obviously these were cases of congenital cataract) than in older patients. In patients above 50 years of age, there was hardly any correlation between the quality of binocular vision and age. The time which elapsed between first and second operation had little influence. The authors feel that operation of the second eye should be encouraged, as the chances of useful binocular vision are good and the advantages of it outweigh any other consideration.

Ogle, Burian, and Bannon [259] attacked a problem long vexing those interested in the mechanism of binocular vision, the problem of unilateral aplakia corrected with contact lenses. Unquestionably, a substantial amount of aniseikonia remains and binoc-

ular vision must remain defective. Still, patients have been reported as being able to wear contact lenses with comfort and with restoration of binocular vision. The practical value of the contact lens correction is beyond question and the use of contact lenses "justified even if the criterion of success, from a clinical point of view, were simply the subjective benefit derived by the patient." But this subjective criterion, our authors tell us, is not the only one. "Favorable reports do not necessarily imply a cure. Too much depends on one's level of satisfaction. . . ." (One must admire the authors for their pursuit of perfection. Most of us poor practitioners are satisfied once the "level of [the patient's] satisfaction" has been scaled. Only if a patient is uncomfortable or not fully satisfied should one try further, and in this case correction of aniseikonia should surely be tried.)

Lieb and Guerry [260] have, in monocular aphakia, very favorable experience with the anterior chamber acrylic lens. Visual acuity ranges between 5/5 and 5/15, stereopsis is restored, divergent strabismus sometimes corrects itself. In fact, one 16-year-old patient saw 5/4 with the lens and read Nieden 2 without reading addition.

Gasteiger [261] is certainly not as enthusiastic. He saw dystrophy, infection, even sympathetic ophthalmitis, and the number of patients with full visual acuity was smaller percentagewise than after simple cataract operation. Only in young people where stereoscopic vision is a factor should this operation be recommended.

Carter,[262] whose excellent review of the literature on fixation disparity was mentioned in last year's Review, described in a second paper his apparatus and procedure for studying this phenomenon. He uses two techniques—central and peripheral binocular fixation. He came across a constant error factor in aligning a binocularly and a monocularly seen line, similar in magnitude to that found by Emsley (1946) in monocular vernier alignment experiments. The reason for this constant error could not be ascertained. (I expect and hope that more installments will follow.)

IX. Accommodation, Vergences, and Miscellaneous Topics

An outstanding piece of clinical research by Calmettes, Deodati, Huran, and Bechac [263] deals with the depth of the anterior chamber in emmetropes and ametropes and the influence of accommodation upon it. The authors used an attachment to the Zeiss slit lamp, described by Jaeger (1951-1956), to measure the depth of the anterior chamber. (The instrument is based on a simple optical coincidence principle.) The authors found that the chamber reaches a maximum depth value in the third decade of life and is shallower in women than in men. It increases with increasing myopia but relatively more in the moderate degrees of it. In accommodation they found a decrease of depth of the anterior chamber of 0.10 to 0.50 mm. in most of their prepresbyopic patients. Atropine increased the depth of the anterior chamber in 10 of 15 cases, decreased it in none.

Armaly and Burian [264] found that accommodation affects the tonographic tracing in young subjects with normal eyes. The facility of outflow, the so-called C-value, increased when the examined eye was accommodating. By what mechanism this change came about, the authors were unable to tell as yet.

Alpern, Ellen, and Goldsmith [265] recorded an electric potential over the region of the ciliary body during the process of accommodation from far-to-near or from near-to-far. The first process produced an increase of negativity of the electrode, the latter an increase of positivity. The authors could not come to any definite conclusion regarding the source of these potentials.

Using an optometer type instrument, Alpern [266] was able to determine the changes of the dioptic power of the eye while fixating a row of letters as steadily as possible. The variability decreased almost fourfold, while the intensity of retinal illumination

increased. A sharp transition became manifest at 1 troland retinal illumination, indicating that there was a discontinuity from scotopic to photopic vision at this level. Cycloplegia eliminated the variability. When the eye is in focus, one can assume that the contour, the border between white and black, represents a slope of greatest steepness and intensity. Too much or too little accommodation decreases this optimum slope. The author believes that this achievement of the best possible sharpness of contour by constant oscillation is possibly one of the stimulus components of accommodation. (Alpern's theory would also explain why the presentation of a blurred target represents actually no stimulus to accommodation.)

It seems that Campbell, Westheimer, and Robson [267] are not in full agreement with this hypothesis. They find that the method does not have "sufficient time resolution to obtain the clear picture of the fluctuations that is necessary to evaluate the hypothesis." Their own records show a slower frequency range of fluctuations of accommodation of 0.3 cps and a faster one of 2 cps. The slower components increase in amplitude when the subject is presented with an empty field or when the pupil size is diminished. The authors feel that not these but only the fast oscillations could be the ones which offer directional clues to the accommodation system but that further study of the nature of the feedback of information is necessary.

Experiments to determine the near accommodation level with the crossed cylinder and grid target confirmed, after Westheimer,[268] the conclusion that the "accommodative stance" in a near-viewing situation depends on many factors. The author believes that apparent spatial localization plays a major part in the establishment of the accommodative level. "The crossed-cylinder test is probably excellent to determine whether a patient is over- or underaccommodating for the distance. . . . The immediate response of whether the horizontal or vertical lines are clearer will give the information. . . . Even during subsequent attempts by means of lenses to make both sets of line clear . . . he will usually not change his accommodation to retain clarity of one or the other sets of lines." Westheimer suggests a small change in the routine of the test which, I think, is worth trying.

Two papers by Alpern [269,270] deal with the relation of ocular vergence to accommodation. Alpern repeated the well-known experiments of Ittelson and Ames and confirmed their finding that the eyes converge when target size is increased, even if there is no change in the stimulus to accommodation. The convergence is most probably related to increase of perceived size, not to any change of the actual state of accommodation. Another set of the author's experiments concerns itself with the relation between accommodative vergence and accommodative effort. The results suggest that it is the actual accommodative response which is responsible for the change of vergence, not any change of the stimulus to accommodation.

A paper by Kittel,[271] while containing an undue amount of speculative material, is of interest. He tested the near phoria of patients with the old Bielschowsky heterophorometer and with one of the many modern near-vision testers (the one made by Oculus) and found that in people with asthenopic complaints (he designates their eyes as having "vegetative dystony") the two measurements did not agree. They did in normals. It was, however, possible to produce similar discrepancies in near heterophoria even in normals if homatropine or pilocarpine was instilled before the test and, thus, the normal synkinesis of accommodation and convergence disturbed. People with asthenopia, the author concluded, probably suffer from such a disturbance of the accommodation-convergence relationship. (Of course, the results also show that each phoria-testing device has its own "instrument errors" and that it is hardly justified to compare values attained by different observers with different methods. The sound-

est clinical practice is to stick to *one* technique and to develop one's own standards of normal values.)

Sabin and Ogle [272] measured the relation of accommodative convergence to accommodation after instillation of different drugs. Phenylephrine had little effect on accommodation and caused no change in accommodative convergence. The linear relationship between accommodative convergence and change of stimulus to accommodate was also maintained after instillation of pilocarpine or physostigmine. The results with miotics cast some doubt on the probability of Fincham's hypothesis, according to which the Stiles-Crawford effect could contribute as a stimulus to accommodation. This effect could not reasonably account for the author's results, since the pupils were too small for its operation.

The usual designation in the literature for the association of accommodation with accommodative convergence is AC/A or (A-C)/A. We find in Parks' [273] paper the symbol A:AC. (It is hard to decide which designation is the more logical, though "AC/A" should be preferable. If accommodative convergence is greater than normal for a given value of accommodation, one can then speak of "increased AC/A ratio, AC being in the numerator of a fractional symbol. Parks' A:AC ratio, with AC in the denominator, actually becomes smaller when esotropia or esophoria become "exaggerated" at close range.) Parks found abnormal A:AC, i. e., exaggerated esotropia four times more often in acquired than in congenital esotropia. He considers this a factor of equal importance with hypermetropia in the etiology of convergent squint. In exotropia the same exaggerated convergence helps in the maintenance of binocular single vision at near. Bifocals control the symptoms of abnormal A:AC in esotropia and DFP normalizes it (while it is given, in young children; more permanently in those 7 years or older). The exaggerated "eso" which is caused by an abnormal A:AC is compensated by fusional divergence which in children 7 years or older can be assisted by orthoptic (dissociative) exercises.

Manas [274] finds that visual training (whatever that means) increases the AC/A ratio. Thus, he concludes, it cannot be a "unique biological constant," but is "a calculable variable denoting the change in convergence per unit change in accommodation at the moment."

The relationship of the accommodation which is induced by convergence to the actual amount of accommodation can be expressed in the form of a similar ratio, CA/A. The desirable numerical value of this is determined, according to Kent,[275] by a simple formula: $\frac{1}{\text{PD:(in cm.)}}$. Kent's results show that there are subjects who accommodate more and others who accommodate less than this desirable amount. Those who belong into the first group must undo some of their convergence accommodation; the second group is in need of supplementary accommodation. His data show that in those whose amplitude of accommodation is 10 D. or more, convergence often is sufficient incentive to accommodation and might provide the principal stimulus for it.

Berens, Brackett, and Taylor [276] advised the use of an accommodation card (devised by Berens and Fonda), of a prism bar (devised by Berens), and, when needed, of clip-on plastic spheres or prisms (devised by Berens and Taylor) for home divergence exercises at close range. The exercises are meant for patients who are unable to maintain fusion when accommodating on small print or for patients (usually young children who are frequently found to be slow readers) who manifest overconvergence on ophthalmographic studies.

Flom [279] filmed the eye movements during the cover test. In some cases he found that when the preferred eye is covered, the other shows a small movement (a "flick"). These persons have, as a rule, comfortable binocular vision, a large heterophoria, fair to good stereoacuity, and a small "angle of anomaly." (Since in the language of most of us only people with so-called anomalous

retinal correspondence can have an "angle of anomaly," Flom obviously means something else than most of us do when using this term. Unfortunately, he does not explain.)

Mackensen [278] studied the normal horizontal gaze movements by an electro-oculographic method and found that their speed first increases, then falls in the form of a sinusoidal curve, reaching its maximum in the middle of the excursion. He confirmed the fact that voluntary influencing of the speed of gaze movements is impossible and that the maximum speed increases when excursions become larger.

People with heterophoria (be it natural or artificially introduced) generally note decreasing separation of double images and experience increasingly faster fusion when the fixation target is presented repeatedly and with sufficiently short intervals. Experiments of Holland [279] showed that it takes an interval of 8 to 10 seconds between exposures before fusion regains its original, relatively slow, time value. The fact was already known to Hering, and its cause must be a residue of innervation or of tonic muscular contracture. This tonic residue will explain why people with heterophoria are so relatively efficient with binocular vision under ordinary circumstances.

Bennett, Wells, Binder, and Brecher [280] examined the time course of the fusion movements. They found it to take about 1 second, including latent period. They found no correlation between the velocity of the fusion movement and the degree of heterophoria. Some subjects with large phorias were fast fusers, others with small phorias were slow fusers.

Jaensch,[281] one of Bielschowsky's most prominent pupils and a foremost authority on ocular motility, discussed a problem which seemingly has achieved some actuality in Germany (fortunately not yet in this country), the problem of the so-called "sight schools" (*Sehschulen*) in which modern pleoptics should be applied for the treatment of amblyopia. The name itself evokes unpleasant associations, being reminiscent of the eye-exercise racket which in Germany for a long time flourished under the same name. He is also very much against the proposed incorporation of amblyopia treatment among the activities of the so-called *Heilpaedagogen* (literally, health teachers), and even more opposed to plans to place unilaterally amblyopic children into sight-saving classes, together with other children who for all kinds of ocular pathology see with *neither eye* more than 20/100 to 20/400. Jaensch is probably right that this must produce a psychologically untenable situation.

(Though not strictly belonging into the area to be covered in this Review, I want to mention a paper by Stanley-Jones [282] about "Cybernetics of Ocular Movement" and especially his discussion of coal miner's nystagmus. It is a pity the author wants to introduce the insipid word "refection" to replace the possibly slangish but much more expressive term "feed-back.")

It is peculiar that such questionable entities as "spiral" and "tubular" visual fields still should hold the attention of seriously minded clinicians. Maybe the latter are a symptom of "hysteria," the former of "neurasthenia," but one wonders if that really matters. Schlaegel [283] presented a statistical analysis of 18 cases found in a survey of 800 unselected eye patients, and one is glad to know that he also agrees that "spiral" visual fields are merely the result of tiring and inattention and have no diagnostic significance.

Kent and Schlaegel [284] studied some cases with hysterical tubular visual fields. It seems they wanted to trap their patients' subconscious with "sexual" and "scoptophilic" (my great Webster does not carry the term) words and also to measure their autonomic reactions by registering their galvanic skin response. For the first part of their study, they still need "more data" (so why did they not wait with publication?) and as far as the second part is concerned, the skin response showed that their patients reactivity was greater than that of normals

to nonsexual and nonscoptophilic words as well (which I am glad to know). The study was supported by a research grant from the Institute of Neurologic Diseases and Blindness, Public Health Service (in other words, with your tax dollar and mine).

Oppel [285] does not believe that the infant is born with a tubular visual field. In fact phylogenetic considerations contradict such an assumption. He thinks rather that the newborn in the beginning has undifferentiated peripheral light-and-dark vision only with central vision missing. To this at first vision of motion and later peripheral and central form vision is added. Central fixation starts falteringly in the 8th to 16th week, improves up to 26th week, while in the second half of the first year of life central vision slowly gains its ascendancy. His beautiful diagrams, modeled on those of the unforgettable Traquair, show how the "mountain of vision emerges from the sea of darkness."

"Haidinger's brushes" were for about a century an item of textbooks, at best a psychophysiologic curiosity. Goldschmidt, of New York, rekindled interest in them some 10 years ago, suggesting the use of rotating brushes as a clinical test of macular function. In the last few years mushrooming pleoptics laboratories turned to Cüppers' coordinator, which is actually a reinvention of Goldschmidt's instrument. The brushes are now brought to attention once more in another, entirely different, connection by Ratliff,[286] one of the original workers on the problem of the fading stationary retinal image. He believes that the rapid fading of the Haidinger pattern, when mediated by a stationary polarization set-up, is but an example of the disappearance of a stationary retinal image.

A paper by Donahue [287] relates on some current concepts about headaches and deserves to be mentioned in this Review. The author reaffirms the classic observations by Edward Jackson and Cogan who found that persons with small amounts of hypermetropia and astigmatism might have more severe symptoms of headache and "eyestrain" than people with large refractive errors. "It is not so much the error of refraction or muscle imbalance that is responsible for headache and other symptoms as the effort made to overcome the handicap." Donahue makes his patients stop after every 50 minutes of concentrated work to relax for ten minutes. This relieves or even prevents ocular headaches. (The contents of that notorious book, "The Art of Seeing," by Aldous Huxley, were thus not complete nonsense. "Palming" and "sunning" and so forth *do* have some beneficial effect—not in themselves but simply by introducing a "pause that refreshes.")

The venerable Dr. C. Rambo,[288] of India, in a Letter to the Editor of these ARCHIVES, asked American ophthalmologists not to use the antiquated foot system of designating visual acuity, at least at international meetings. "It takes a good deal of calculation that is troublesome . . . to translate the unscientific 20/180 and other foot figures into something understandable. . . . May I request those . . . speaking at the Congress to practice the use of the metric system."

Professor Geppert,[289] of the Max Planck (formerly Kaiser Wilhelm) Gesellschaft, in Germany, spoke before a group of ophthalmologists on statistical methods in biology and medicine. Her lecture is easily understandable even to nonmathematicians. To those who are able to read German, this lecture can be warmly recommended as an introduction. It cannot be abstracted or discussed in this type of Review; it should only be brought to the attention of its readers.

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Correspondence

RETINAL DETACHMENT SURGERY: AN ENFOLDING OF THE SCLERA

To the Editor:—In the August, 1958, issue of the A. M. A. ARCHIVES OF OPHTHALMOLOGY (60:247, 1958), Dr. James S. Shipman, in his article entitled Retinal Detachment Surgery: An Enfolding of the Sclera," described a modification of scleral shortening. He states as follows: "In my modification two incisions are made instead of one. . . ." He then goes on to say, "The incisions are now carried deeper through the outer three-fourths of the scleral coat. The anterior and posterior edges of the two incisions are then undermined for about 1 mm., leaving the strip of full thickness of sclera between."

Actually, this is the procedure of "Lamellar Undermining," described by me together with my late colleague, Dr. Karl Rubner, in the *American Journal of Ophthalmology* (41:633 [April] 1956). In this article, we gave full credit to Mueller, Lindner, Dellaporta, Blaskovicz, Paufique, and Hugonnier, as well as Schepens, for their contributions in the development of modern scleral shortening. Dr. Rubner and I merely substituted the partially resected or undermined scleral strip for the polyethylene tube of Schepens. To quote directly from our paper (page 634), ". . . each edge of the lamella was undermined for a distance of about 1.5 mm. toward the middle of the strip, leaving the lamella attached to the sclera along a one mm. central strip."

Since 1956, the reference to our work has found its way into Fasanella's "Management of Complications of Eye Surgery" (Philadelphia, W. B. Saunders Company, 1957, p. 255) wherein Dr. Pischel discusses the various scleral shortenings.

Again, in the March-April, 1958, issue of the *Transactions of the American Academy of Ophthalmology and Otolaryngology,* Dr. Kronfeld, in his contribution to the Symposium on Scleral Resection Procedures, states, "A strong trend is to give more bulk and solidity to the inward protruberance. This is the aim of the various infolding operations in current use. The tendency is to combine the infolding with the creation of raw surfaces in order to promote an active healing process. That is the principle underlying the "Lamellar Undermining" of Chamlin and Rubner (No. 5), which, at the time of this writing, is the operation of choice for many surgeons who are actively engaged in the surgical correction of retinal detachment."

Dr. Kronfeld's paper, of course, was based on his talk at the October, 1957, meeting of the Academy of Ophthalmology and Otolaryngology, in Chicago.

In view of the above facts, it is difficult for me to understand how it could have escaped Dr. Shipman's notice, at least in the research connected with publication of his article, that this procedure had already been described and quoted in standard ophthalmological literature for over two years prior to his date of publication.

MAX CHAMLIN, M.D.
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To the Editor:—I regret very much that I did not know of Dr. Chamlin's publication of "Lamellar Undermining" before I gave my talk on the retinal detachment panel at Section on Ophthalmology of The American Medical Association meeting, in San Francisco last June. I apologize sincerely for my negligence in not reading the literature more carefully and giving Dr. Chamlin credit for reporting earlier a procedure almost identical and certainly similar to that which I later devised and did on about 25 cases without the knowledge of his report. However, in my defense, I would like to say that the report I made was more or less of an informal preliminary nature. I plan to present a more thorough

and accurate report of this procedure with diagrams at a later date, and it was for this reason that more references and bibliography were not given.

Certainly, I am aware of the pioneer work on retinal detachment and scleral shortening which was done by Müller and Lindner, to whom I am personally greatly indebted for a great deal of my interest in and my small knowledge of retinal detachment surgery. I am also aware of the work of Weve, Dellaporta, Blascowicz, and Schepens. I could add many others, such as Pischel, Meek, Kronfeld, Everett, and Shapland of London, whom I saw do the first "reefing procedure" that I had seen for shortening of the sclera, at Moorefeld's Hospital in London in 1950, during the International Congress meeting there. Finally, I give credit to my preceptor, the late Dr. B. F. Baer Jr., who gave me the opportunity to do my early retinal detachment cases and encouraged me to do more.

Indeed, it was not my purpose to take any credit for myself or away from any other person when I made the brief talk that I did at the Section Meeting in San Francisco. I only meant to mention a method of scleral shortening that we had found to be relatively simple and successful, which we had been stimulated to try as a result of seeing Rolet's movie at the Academy in 1956.

Since reading Dr. Chamlin's article on "Lamellar Undermining," I find that there is a slight difference in his technique for undermining, namely, he undermines the strip of sclera in the center leaving a very narrow base, and we undermine the anterior and posterior edges of the sclera adjacent to this strip. We leave the full thickness of the sclera attached at its entire base and fold it all in by tying the sutures over this.

Again I wish to apologize for my oversight and apparent neglect in not giving Dr. Chamlin credit for his very ingenious procedure. Certainly, we have room for all and for much more effective procedures to relieve this very baffling and difficult eye condition.

This mistake of mine reminds me of what Dr. William Zentmayer once said to me, "Shipman, never claim credit for any procedure until you have searched the literature for years back. Even then someone will find that the same thing or something very similar was done by someone else over a hundred years before you did." My apologies to Dr. Zentmayer for not heeding his advice and again to you, Dr. Chamlin.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Harold G. Scheie, M.D., Chairman
William E. Krewson 3d, M.D., Clerk

Dec. 11, 1958

Spontaneous Recovery in a Case of Superior Oblique Tendon Sheath Syndrome of Brown. Dr. Francis Heed Adler.

The syndrome described by Dr. Harold Brown, in 1950, known as the superior oblique tendon sheath syndrome, consists of an apparent inferior oblique paralysis on a congenital basis. It can only be distinguished from a true inferior oblique paralysis by applying the forced-duction test. The globe cannot be passively rotated above the midline in the field of action of the inferior oblique muscle. Various operative procedures have been tried without much success. The result of these has generally been to free the globe so that it could be passively rotated upward, but in most cases the patient cannot voluntarily move the eyes in this direction any better than before operation.

Costenbader and Albert (A. M. A. Arch. Ophth. 59:607, 1958) reported a case with spontaneous cure. I am putting on record a similar case. The child, 4 years of age, was first seen Sept. 8, 1955, with a typical picture of a left inferior oblique paralysis. I advised doing a forced-duction test under anesthesia and deciding at that time what operative procedure to carry out, depending upon whether or not this was found to be a true Brown syndrome. This advice was not accepted, and the parents decided to do nothing about the condition. The child was seen again on May 26, 1958, no treatment having been given in the meantime. The eyes were straight in all positions of gaze, there being no sign of any left inferior oblique paralysis remaining.

While it cannot be stated with certainty that this was a true superior oblique tendon sheath syndrome, it indicates that spontaneous recovery is possible in cases either of this syndrome or of inferior oblique paralysis. Immediate operation is therefore not indicated and, in view of the uncertain operative results, should probably be deferred until these children are older.

Studies on Antibody Production in Rabbit's Eye. Dr. Michael I. Wolkowicz, Dr. Joseph W. Hallett, and Dr. Irving H. Leopold.

1. *Antibody Formation in Vitro After Intraocular Injection of Typhoid Bacilli.*—The study of antibody formation by the uvea in vitro is an outgrowth of our interest in uveitis. Those data can influence our thinking in regard to the etiology of uveitis and our therapeutic approach.

This work is based on previous studies made by Witmer on experimental uveitis, on our studies on Cx-reactive protein, on the work of A. Fagraeus and others on antibody formation, and on the studies by Coons and his associates on antigen tracing by means of fluorescin-conjugation technique.

The laboratory method consisted of injecting a chosen antigen (standard typhoid-paratyphoid vaccine) intraocularly by different routes and keeping the uveal fragments in culture media. The antibody titers of the successive culture tubes represent the antibody activity of the given fragment. The uveal tissue production of antibodies could be further protentiated by increasing the antigenic concentration.

Typhoid "H" proved to be a more stimulating antigen by forcing the uveal fragments to produce antibody titers above the blood serum level.

Uveal tissue, where living cells were destroyed by immersion in formalin, showed a reserve of antibody deposits. The origin of those agglutinins is still uncertain.

Further concentration of Typhoid "H" suspension produced higher peaks of antibody titers but also earlier exhaustion.

Lens System Developed for Water to Air Vision in the Submerged Eye. DR. T. D. DUANE (by invitation).

A Navy project required the circumvention by the submerged human eye of the water-to-air total internal reflection when placed 7.8 cm. from the interface separating the media.

A lens system was developed, and the reasoning leading to the evolution of the final product, a 16 D. Plano-Conven lens with a superimposed 52.5 D. loupe, was presented. With this combination of lenses, subjects were able to see through the interface with 6/6 acuity, a field of vision of 20 degrees, and a full range of accommodation.

News and Comment

PERSONAL

Dr. Bradley Ralph Straatsma.—Dr. Bradley Ralph Straatsma has been appointed Associate Professor of Surgery at the School of Medicine of the University of California at Los Angeles. He will succeed Dr. S. Rodman Irvine as Chairman of the Division of Ophthalmology. Dr. Irvine will remain as Clinical Professor of Surgery.

Dr. Lalit P. Agarwal.—Dr. Lalit P. Agarwal has been appointed Professor and Head of the Department of Ophthalmology in the All-India Institute of Medical Sciences, New Delhi, India. Any correspondence with Dr. Agarwal should be sent to that Institute, Ansari Nagar, New Delhi, India.

GENERAL NEWS

Information Exchange Established.—The National Committee for Research in Ophthalmology and Blindness has established a confidential information exchange for groups seeking scientists, physicians, or technical personnel interested in research in ophthalmology and blindness. Institutions or persons interested may secure information from the Committee office, 406-C South Boulevard, Evanston, Ill.

Walter W. Wright Lectureship Established.—Dr. Walter W. Wright, University of Toronto Professor Emeritus of Ophthalmology, has been honored by a lectureship in his name established with funds raised by Department of Ophthalmology staff members, former students, and friends.

Dr. Wright conceived and developed the postgraduate training of physicians in eye diseases, the first such training in Canada, which began at the University of Toronto in 1941. Since then 65 specialists have been trained and are now practicing from coast to coast. This project still holds Dr. Wright's special interest. He is also consultant to the Canadian National Institute for the Blind, the Toronto General Hospital, and the Hospital for Sick Children.

He joined the University of Toronto staff in 1908 after graduating four years earlier and, in 1914-1915, did postgraduate work at the Royal London Ophthalmic Hospital. He then served as an ophthalmic specialist in the Canadian Army Medical Corps at Bramshott Hospital, England, and in France and later at Westcliff Hospital, Folkestone, Kent. He returned to the University in 1921, and headed the Department of Ophthalmology from 1941 until retirement in 1946. Dr. Wright was the first to report on the use of living sutures in the treatment of ptosis, in 1922, and in later years was active in stressing the necessity for early treatment of strabismus in infants. A renowned wicket-keeper in his younger days, Dr. Wright was a member of the Canadian cricket team versus the United States in 1905, and he toured England in 1910.

The first Walter W. Wright Lecture was scheduled to be given by Prof. Norman Ashton, ophthalmic pathologist of the Institute of Ophthalmology, London, England, speaking on "A New Approach to the Problem of Diabetic Retinopathy," at the Academy of Medicine on Feb. 27. In Britain, Prof. Ashton's research achievements have earned him the Nettleship Medal (1954), the Middlemore Prize (1955), and membership of the Royal College of Physicians of London. In 1957, he became the first non-American to receive the Proctor Medal of the American Association for Research in Ophthalmology.

ANNOUNCEMENTS

Postgraduate Courses for Ophthalmologists.—The Institute of Ophthalmology of the Americas announces that the second series of postgraduate courses for ophthalmologists will be given from Sept. 14-Nov. 25, 1959.

Courses will be offered in the following subjects: advances in ocular prosthesis; anomalies of extraocular muscles, including ptosis; biomicroscopy; biomicroscopy with use of near ultraviolet, cobalt blue, and polarized light; clinical bacteriology; complications of ophthalmologic surgery; contact lenses; electrophysiology and applied physiology of the eye; enucleation and evisceration; fundamental principles of orthoptics; glaucoma; gonioscopy and tonography; keratectomies and keratoplasties; lacrimal sac surgery; low vision aids; ocular biochemistry; ocular geriatrics; ocular microbiology; ocular neuro-ophthalmology; ocular photography; ocular radiology; ocular therapeutics; ophthalmoscopy; pathology; perimetry; physiological optics; plastic eye surgery; pleoptics and macular function testing; psychosomatic factors in ophthalmology; radioisotopes in ophthalmology; recent advances in cataract surgery; refraction; retinal detachment, and surgery of the orbit.

Further information regarding the Courses may be obtained by writing to Mrs. Tamar Weber, Registrar, Institute of Ophthalmology of the Americas, New York Eye & Ear Infirmary, 218 2d Ave., New York 3.

Wayne State University Postgraduate Course.—The Department of Ophthalmology of Wayne State University College of Medicine will give nine months' training in basic ophthalmology beginning Sept. 21, 1959.

Six mornings a week are spent in lectures and laboratories. Each afternoon students are assigned to eye clinics of affiliated hospitals. A fundus clinic is held weekly, also one on muscles.

Students are given 120 hours of training in physiologic optics, 122 hours in histology and pathology, 60 hours in biochemistry, 40 hours in neuroanatomy.

Tuition is $300. Brochures on the basic sciences course will be mailed upon request. For further information write to A. D. Ruedemann, M.D., Chairman, Department of Ophthalmology, 690 Mullett St., Detroit 26.

Vacancies for Residents at the Instituto Barraquer.—This is to advise all doctors who wish to improve their knowledge in ophthalmology that a Concourse of Merits will start on Feb. 1, 1959, in order to cover four vacancies for residents in the Instituto Barraquer.

The application and other documents may be sent to this institution and will be admitted until Sept. 30, 1959.

The applicants should have the minimum following qualifications, according to the rules of the Institute: Degree of Medical Doctor; one year's practice in the specialty, in a clinic or an accredited institution; introduction by two ophthalmologists of recognized scientific standing. The applicants should specify all their aptitudes. Those who have made a stage as a nonresident at the Institute will be given special consideration.

For further information, write the General Secretary, Instituto Barraquer, Laforja 88, Barcelona, Spain.

Oxford Ophthalmological Congress Elects Office-Holders.—The next meeting of the Oxford Ophthalmological Congress, to be held on July 1-4, 1959, will celebrate the 50th anniversary of its foundation.

The following office-bearers were recently elected: Master: Mr. O. M. Duthie, Manchester; Deputy Master: Mr. C. H. Bamford, Derby; Editorial Secretary: Mr. L. P. Jameson Evans, Birmingham; Honorable Secretary and Treasurer: Mr. Ian C. Fraser, Shrewsbury.

The main discussion at the 1959 meeting will be "Ophthalmic Manifestations in Pediatric Practice." One day will be devoted to "Afterthoughts" on their Doyne Lecture delivered by 15 past lecturers.

Basic Science Home Study Courses.—The 1959-1960 Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, which are offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on Sept. 1 and continue for a period of 10 months. Detailed information and application forms can be secured

from Dr. William L. Benedict, Executive Secretary-Treasurer of the Academy, 15 2d St. S. W., Rochester, Minn. Registrations should be completed before Aug. 15.

Course in Practical Perimetry for Office Assistants.—The Ohio State University, Department of Ophthalmology will present a course in practical perimetry for office assistants July 13-15. Registration is limited to persons sponsored by an M.D. Registration will be validated by receipt of a $25 check. On July 16 and 17 a course for ophthalmology secretaries is planned and will familiarize your secretary with terminology, basic facts, the measurement of visual acuity, and the use of the lensometer. The fee for this is $20. Full refund will be made if the registrant is unable to attend.

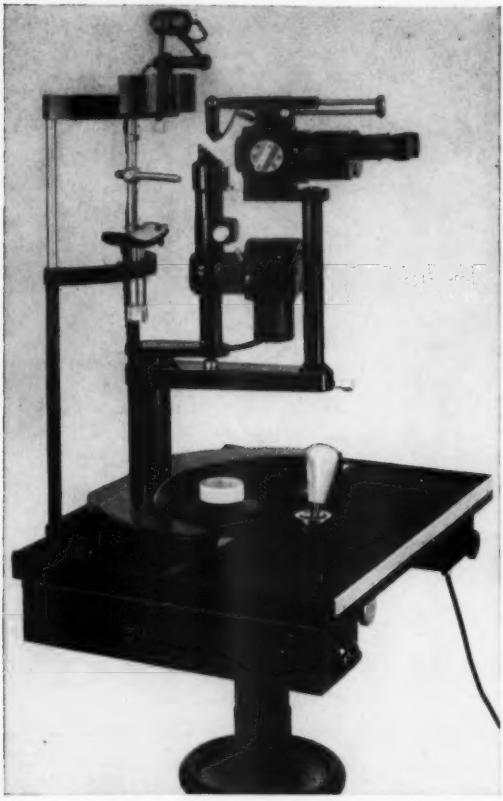
Books

Heredity in Ophthalmology. By Jules François. Price, 8,000 fr. Pp. 876, including index, with 629 illustrations. Masson & Cie, 120 boulevard Saint-Germain, Paris 6e, 1958.

This authoritative volume on heredity in ophthalmology will be accessible only to those who read French, which is a pity, as we are badly in need of a similar authoritative volume in English in this growing and important subject. Fortunately, the French is fairly easy reading, and there are plenty of references at the end of each chapter, a good many of which are in English.

The first part of the book deals with genetics in general and includes a section on the use of statistics. Part II is a general survey of genetics in ophthalmology, and the remainder of the book concerns hereditary ocular diseases and general diseases with ocular manifestations on a hereditary basis. The illustrations for the most part are genetic diagrams, but there are also excellent fundus drawings and photographs throughout the book.

The author is one of the most dynamic living ophthalmologists, who has contributed to almost every field of ophthalmology and plays a promient and responsible part in the organization of many ophthalmic societies. It is truly amazing that he has found the time to produce this stupendous piece of work in addition to his other activities.



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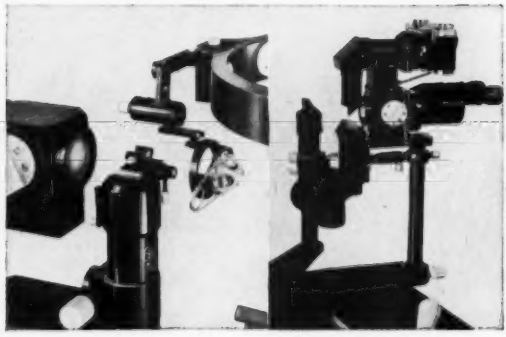

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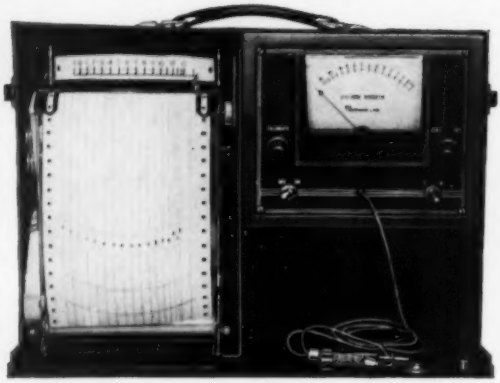

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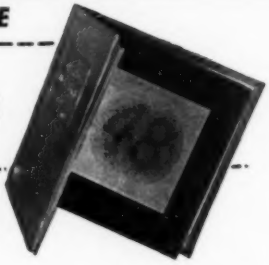

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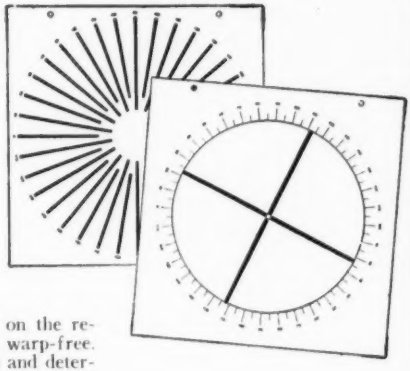

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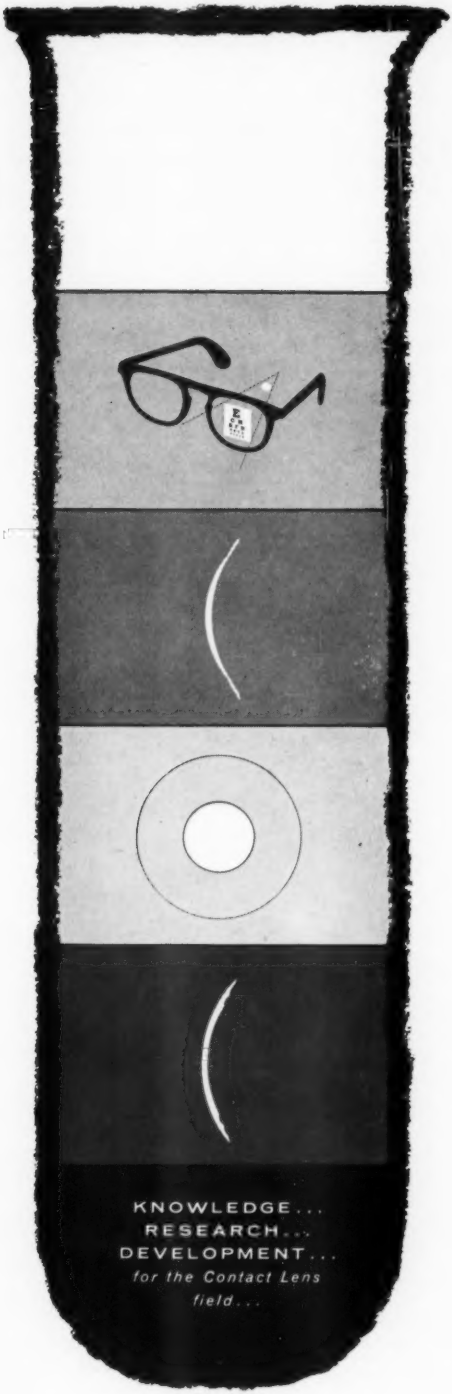

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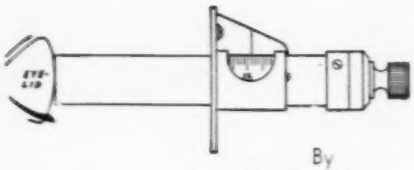

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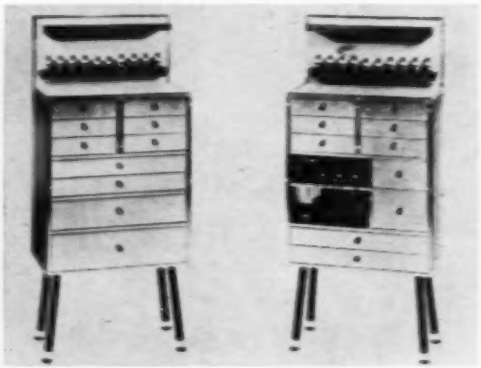

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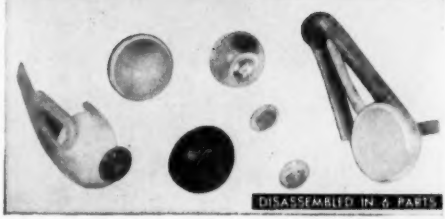

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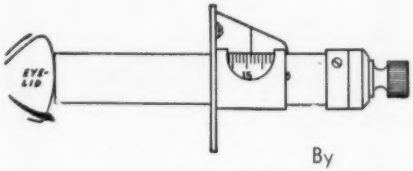

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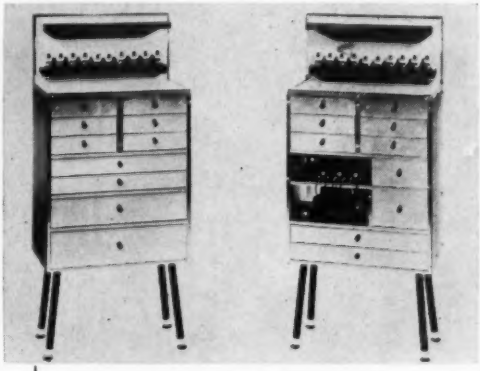

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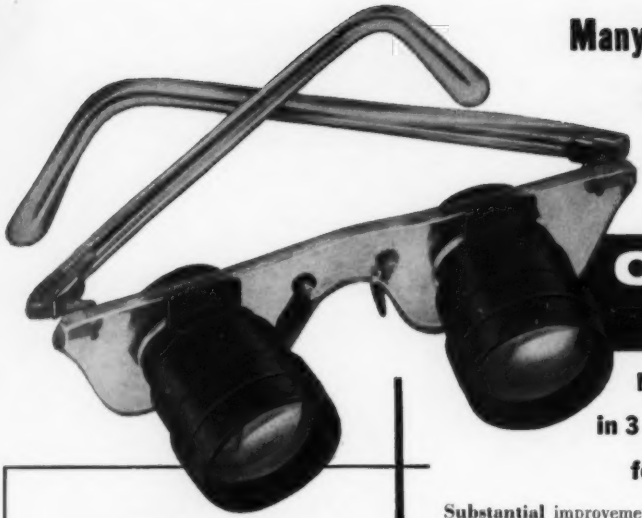

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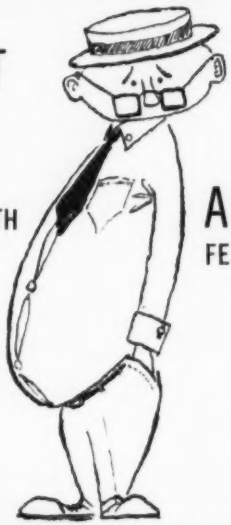

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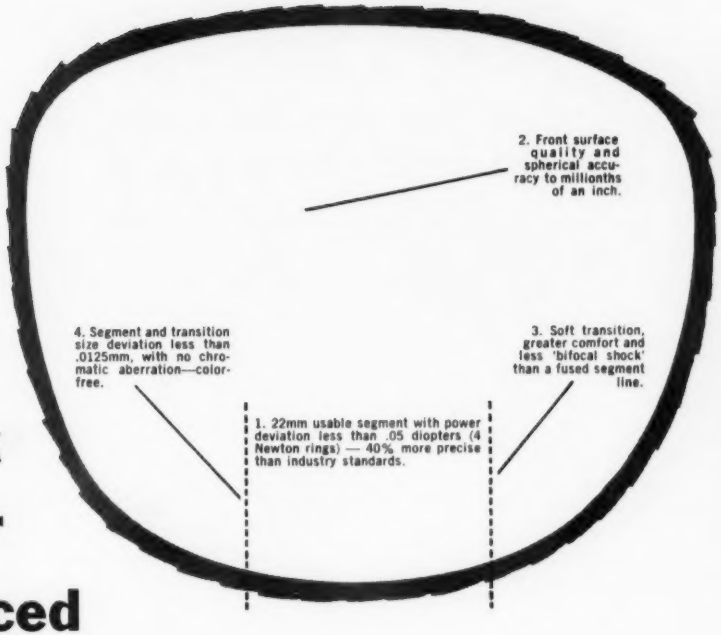
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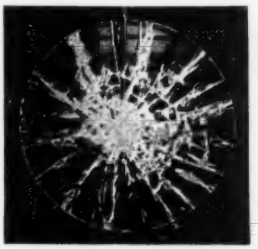

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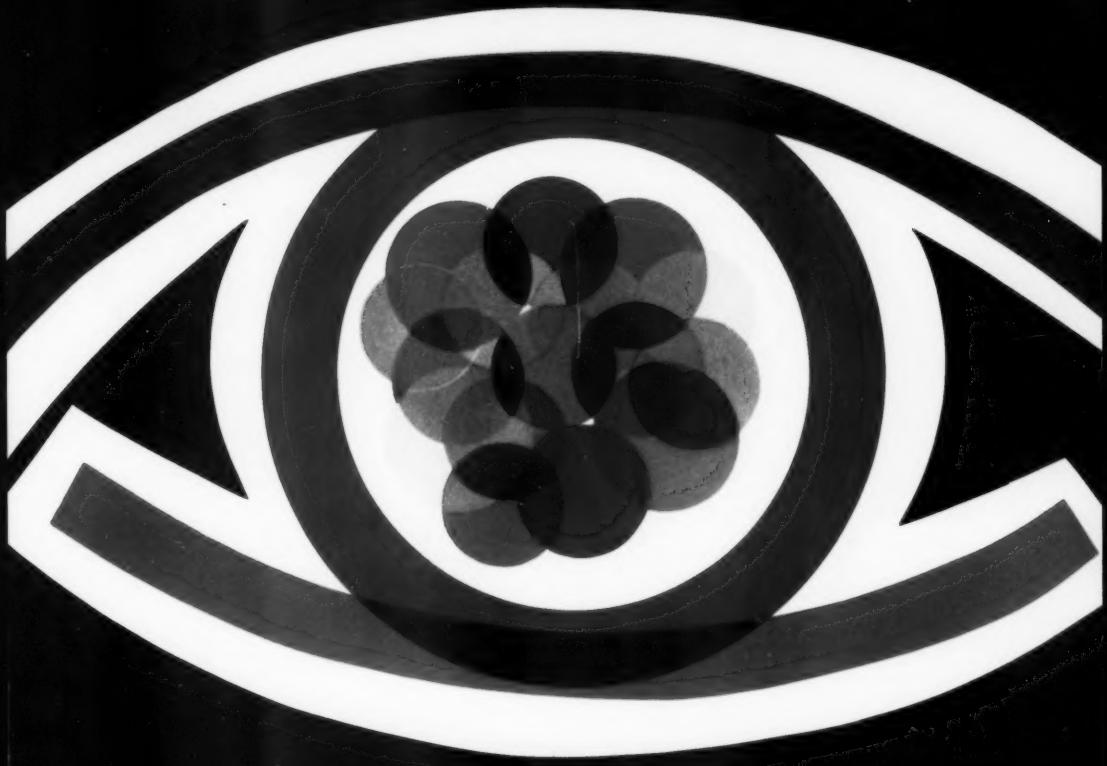

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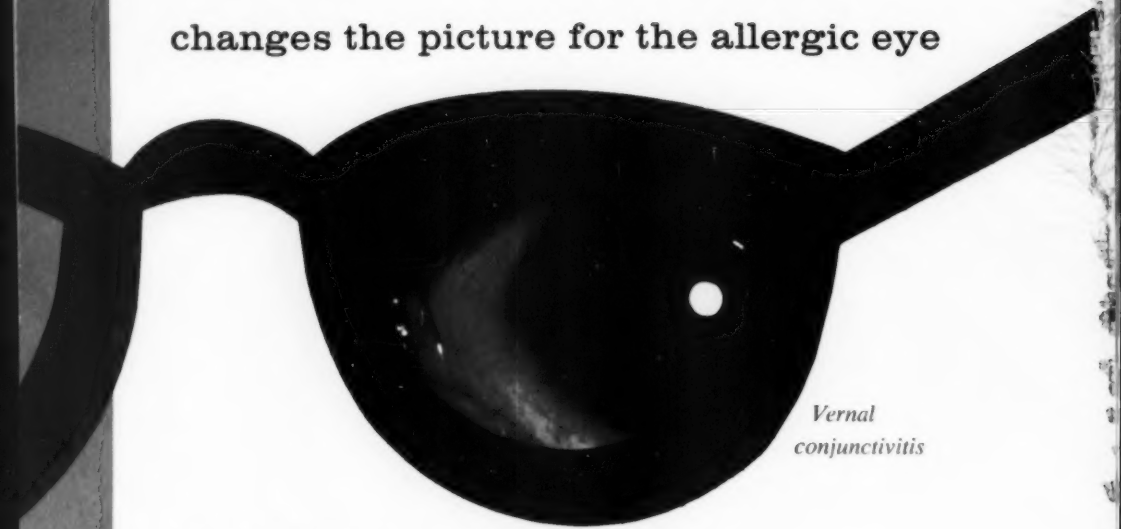

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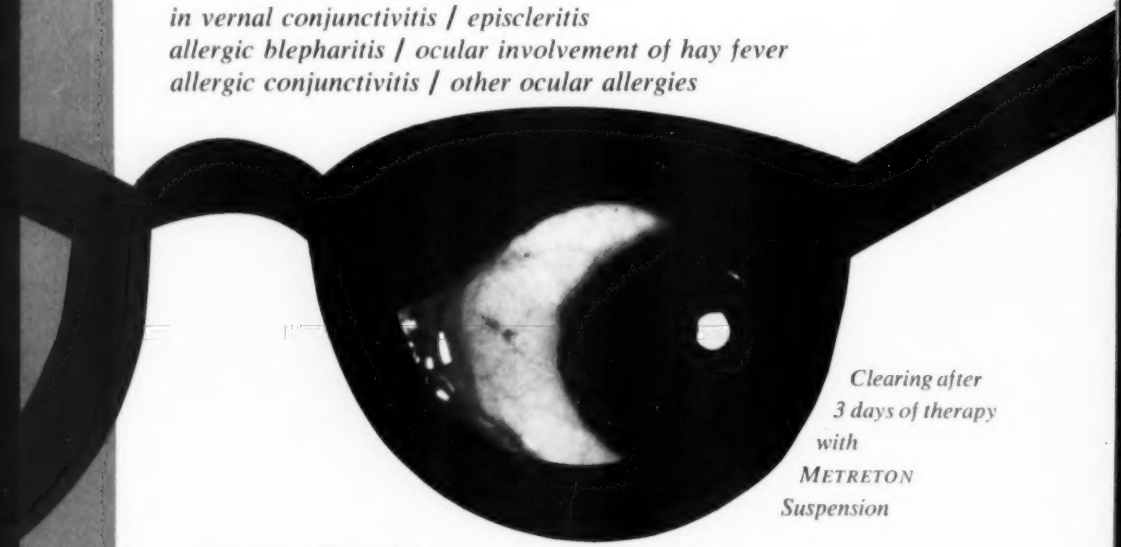

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